

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



AQ

(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079146 A2

(51) International Patent Classification⁷: C07D

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(21) International Application Number: PCT/US02/06581

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(22) International Filing Date: 2 March 2002 (02.03.2002)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

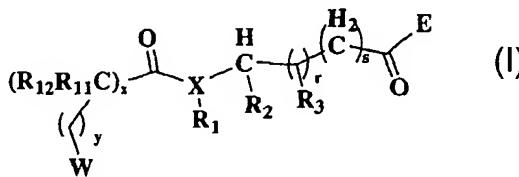
Published:

— without international search report and to be republished upon receipt of that report

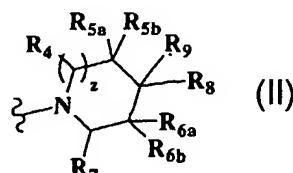
(30) Priority Data:
60/273,206 2 March 2001 (02.03.2001) US
60/273,291 2 March 2001 (02.03.2001) US

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS USEFUL AS MODULATORS OF MELANOCORTIN RECEPTORS AND PHARMACEUTICAL COMPOSITIONS COMPRISING SAME



(57) Abstract: Compounds having the formula (I), and pharmaceutically-acceptable salts, hydrates and prodrugs thereof, in which E is formula (II), X is N or CH, W is -NR₁₆R₁₇, -NR₁₆C(=O)R₂₂, -NR₁₆CO₂R₂₂, -OR₂₃, or a heteroaryl or heterocyclo group as defined in the specification, and R₁ through R₁₂, R₁₆, R₁₇, R₂₂, R₂₃, x, y, and z are as defined in the specification, are useful as modulators of melanocortin receptors, particularly MC-1R and MC-4R.



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**COMPOUNDS USEFUL AS MODULATORS OF MELANOCORTIN
RECEPTORS AND PHARMACEUTICAL COMPOSITIONS COMPRISING
SAME**

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Background of the Invention

Melanocortin peptides, particularly α -melanocyte stimulating hormone (α -MSH), have a wide range of effects on biological functions including feeding behavior, pigmentation, and exocrine function. The biological effects of α -MSH are mediated by a sub-family of G protein-coupled receptors, termed melanocortin receptors. There are four 10 melanocortin receptors: MC-1R, MC-3R, MC-4R, and MC-5R (MC-2R is not a receptor for α -MSH but is the adrenocorticotropic hormone {ACTH} receptor). Activating any one of these receptors results in stimulation of cAMP formation.

MC-1R was first found in melanocytes. Naturally occurring inactive variants of MC-1R in animals were shown to lead to alterations in pigmentation and a subsequent 15 lighter coat color. From these and other studies, it is evident that MC-1R is an important regulator of melanin production and coat color in animals (or skin color in humans). MC-3R is expressed in the brain and peripheral tissues, and knock-out studies have revealed that MC-3R is responsible for alterations in feeding behavior and body weight. MC-4R is primarily expressed in the brain. Genetic knock-outs and pharmacologic manipulation of 20 MC-4R in animals have shown that agonizing MC-4R causes weight loss and antagonizing MC-4R produces weight gain. MC-5R is ubiquitously expressed in many peripheral tissues and in the brain, but its expression is greatest in exocrine glands. Genetic knock-out of this receptor in mice results in altered regulation of exocrine gland function, leading to changes in water repulsion and thermoregulation.

25 Attention has been focused on the study of MC-3R and MC-4R modulators and their use in treating body weight disorders, such as obesity and anorexia. However, evidence has shown that the melanocortin peptides have potent physiological effects besides their role in regulating pigmentation, feeding behavior, and exocrine function. In particular, α -MSH recently has been shown to induce a potent anti-inflammatory effect in 30 both acute and chronic models of inflammatory diseases including inflammatory bowel

disease, renal ischemia/reperfusion injury, and endotoxin-induced hepatitis.

Administration of α -MSH (either i.p. or i.v.) in these models results in substantial lessening of inflammation-mediated tissue damage, a significant decrease in leukocyte infiltration, and a dramatic reduction in elevated levels of cytokines (e.g., TNF- α),

- 5 chemokines (e.g., MCP-1, IL-8) and inflammatory mediators (e.g., i-NOS and ICAM-1), to near baseline levels. Earlier studies had shown that α -MSH acts as an "anti-cytokine" in many acute inflammatory models, in effect antagonizing the pro-inflammatory actions of TNF- α , IL-1 β , and IL-6.

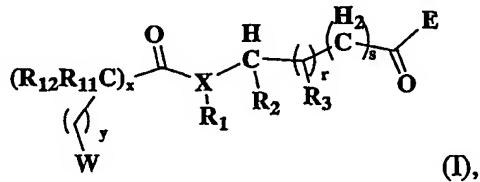
Recent studies have demonstrated that the anti-inflammatory actions of α -MSH
10 are mediated by MC-1R. MC-1R is expressed in cells that are important regulators of the immune response: monocyte/macrophages, neutrophils, endothelial, and mast cells. Stimulation with α -MSH results in a dampening of the inflammatory response in these cells, including inhibition of nitric oxide formation, decreased expression of co-stimulatory molecules and adhesion receptors, and importantly, an increase in the
15 expression of IL-10, a cytokine with potent anti-inflammatory actions. Further studies have shown that MC-1R selective peptides are as efficacious as α -MSH in eliciting an anti-inflammatory response.

The mechanism by which agonism of MC-1R results in an anti-inflammatory response is likely through inhibition of the pro-inflammatory transcription activator, NF- κ B. NF- κ B is a pivotal component of the pro-inflammatory cascade, and its activation is a central event in initiating many inflammatory diseases. In a typical inflammatory response, NF- κ B is activated in response to an inflammatory stimulus and once activated, induces expression of a wide array of pro-inflammatory genes. Activation of MC-1R, and subsequent generation of cAMP and/or decreased production of nitric oxide, inhibits activation of NF- κ B. Thus, α -MSH exerts anti-inflammatory actions through stimulation of MC-1R on cells involved in the inflammatory response and subsequent inhibition of the activation of the pro-inflammatory transcription factor NF- κ B. Additionally, anti-inflammatory actions of α -MSH may be in part, mediated by agonism of MC-3R and/or MC-5R.

The present invention provides compounds useful as modulators of the melanocortin receptors, including selective modulators of MC-1R and/or MC-4R. Melanocortin receptor modulators, particularly MC-1R and MC-4R modulators, are also disclosed in International application Serial No. _____, filed concomitantly herewith by the same inventors and applicant, claiming priority to US patent applications Serial Nos. 60/273,206, and 60/273,291, filed March 2, 2001, titled “*Compounds Useful as Modulators of Melanocortin Receptors and Pharmaceutical Compositions Comprising Same*,” the entire contents of which is incorporated herein by reference.

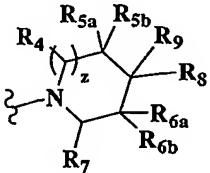
Summary of the Invention

10 The present invention is directed to compounds having the formula (I), useful as modulators of one or more melanocortin receptors,



15 and pharmaceutically-acceptable salts, hydrates or prodrugs thereof,

in which



20 E is ;

X is N or CH;

R₁ is hydrogen or C₁₋₆alkyl or is joined together with R₂ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₂ is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo; or C₁₋₆alkyl or C₂₋₆alkenyl

25 optionally substituted with one to three of hydroxy, alkoxy, halogen, cyano, nitro, trifluoromethyl, amino, alkylamino, aryl, cycloalkyl, heteroaryl, and/or

heterocyclo; or R₁ is joined together with R₂ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₃ is hydrogen or C₁₋₆alkyl or is joined together with R₂ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

5 R₄, R₅, R_{5a}R_{5b}, R₆, R_{6a}, R_{6b}, and R₇ are independently selected from hydrogen, alkyl, substituted alkyl, halogen, hydroxy, alkoxy, keto, aryl, heteroaryl, cycloalkyl, and heterocyclo, or R_{5a} and/or R_{5b}, R_{6a} and/or R_{6b}, are joined together with R₈ or R₉ to form a fused carbocyclic, heterocyclic or heteroaryl ring;

R₈ and R₉ are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, -OR₁₃, -NR₁₃R₁₄, -SR₁₃
10 -S(O)_pR₁₄, -C(=O)R₁₃, -OC(=O)R₁₃, -CO₂R₁₃, -C(=O)NR₁₃R₁₄, -NR₁₃C(=O)R₁₄,
-OC(=O)NR₁₃R₁₄, -NR₁₃CO₂R₁₄, -NR₁₃C(=O)NR₁₄R₁₅ or -NR₁₃SO₂R₁₄; or R₈ and
R₉ taken together form a monocyclic or bicyclic cycloalkyl or heterocyclo joined
15 in a spiro fashion to ring E at C*, provided that R₈ and R₉ are not both hydrogen,
and provided further that when R₈ is -OR₁₃, -(CH₂)_k-aryl or -(CH₂)_k-heteroaryl,
then R₉ is not -C(=O)NR₁₈R₁₉, -CO₂R₁₉, -(CH₂)_mNR₁₈SO₂R₂₀,
-(CH₂)_mNR₁₈C(=O)R₂₀, -(CH₂)_mOR₁₉, -(CH₂)_mO(C=O)R₂₀, -CH(R₁₈)R₁₉, or
-(CH₂)_mNR₁₈(C=O)NR₁₉R₂₁;

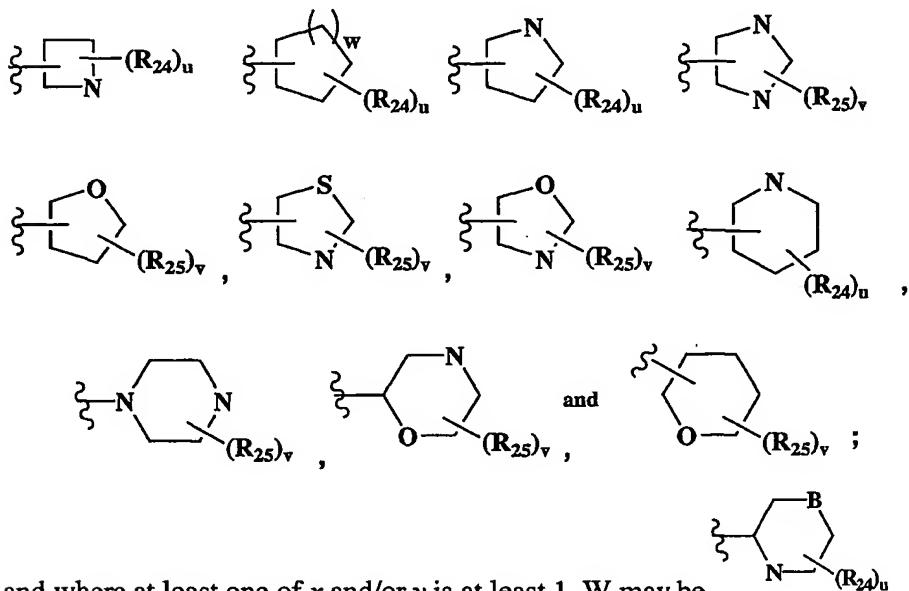
R₁₁ and R₁₂ are selected independently of each other from hydrogen, alkyl, halogen,
20 hydroxy, hydroxylalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl,
cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, and where y is at least 1,
then R₁₁ and R₁₂ may be heterocyclo or heterocycloalkyl, or R₁₁ and R₁₂, when
attached to the same carbon atom, may join to form a spirocycloalkyl ring;

R₁₃, R₁₄ and R₁₅ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl,
25 heterocyclo, or heteroaryl; or R₁₃ and R₁₄, or R₁₄ and R₁₅ may join together to
form a heterocyclo or heteroaryl, except R₁₄ is not hydrogen when joined to a
sulfonyl group as in -S(O)_pR₁₄ or -NR₁₃SO₂R₁₄;

W is selected from:

- 1) -NR₁₆R₁₇, -NR₁₆C(=O)R₂₂, -NR₁₆CO₂R₂₂, -OR₂₃, amidino, and guanidino;

- 2) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said heteroaryl and heterocyclo groups may be substituted or unsubstituted and may have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused thereto; or
 - 3) a ring selected from:



R_{15} and R_{17} are selected from hydrogen, alkyl and substituted alkyl;

R_{18} , R_{19} and R_{21} are independently hydrogen or C_{1-6} -alkyl optionally substituted with halogen:

- 15 R₂₀ is C₁₋₆alkyl, aryl, or heteroaryl;
R₂₂ and R₂₃ are independently selected from hydrogen, alkyl, substituted alkyl, aryl,
heteroaryl, cycloalkyl, and heterocyclo;
R₂₄ and R₂₅ at each occurrence are attached to any available carbon or nitrogen atom of W
and at each occurrence are selected from hydrogen, C₁₋₆alkyl, halogen, substituted
C₁₋₆alkyl, amino, alkylamino, cyano, nitro, trifluoromethoxy, -C(=O)R₂₆,

- CO₂R₂₆, —SO₂R₂₆, —OR₂₆, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R₂₅ attached to two adjacent nitrogen or carbon atoms may join to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R₂₄ or two R₂₅ when attached to the same carbon atom may form keto (=O);
- 5 R₂₆ is hydrogen, alkyl, substituted alkyl, aryl, heterocyclo, cycloalkyl, or heteroaryl, except when joined to a sulphonyl group as in SO₂R₂₆, then R₂₆ is not hydrogen; k and m are independently 0, 1, 2 or 3;
- p is 1, 2, or 3;
- r is 0 or 1;
- 10 s is 0 or 1;
- u and v are 0, 1, 2, or 3;
- w is 0, 1, or 2;
- x and y are 0, 1, 2, 3, or 4; and
- z is 0, 1, or 2.
- 15

The invention is further directed to pharmaceutical compositions comprising one or more compounds according to formula (I). The invention is further directed to methods of treating melanocortin-receptor associated conditions, as defined herein, as well as methods of agonizing or antagonizing the melanocortin receptors, more particularly, MC-1R and MC-4R. The invention is also directed more generally to small molecule inhibitors of MC-1R, and to methods of treating diseases responsive to inhibition of MC-1R using a small molecule according to the invention.

25

Detailed Description of the Invention

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl

groups of 1 to 4 carbon atoms, are most preferred. When a subscript is used with reference to an alkyl or other group, the subscript refers to the number of carbon atoms that the group may contain.

- The term "substituted alkyl" refers to an alkyl group as defined above having one, two or three substituents selected from the group consisting of halo, amino, cyano, keto (=O), -OR_a, -SR_a, NR_aR_b, -(C=O)R_a, -CO₂R_a, -C(=O)NR_aR_b, -NR_aC(=O)R_b, NR_aCO₂R_b, -OC(=O)R_a, -OC(=O)NR_aR_b, -NR_cC(=O)NR_aR_b, NR_aSO₂R_d, SO₂R_d, SO₃R_d, cycloalkyl, aryl, heteroaryl, or heterocycle, wherein the groups R_a, R_b, and R_c are selected from hydrogen, C₁₋₆alkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or C₁₋₆alkyl substituted with halogen, hydroxy, methoxy, nitro, amino, cyano, -(C=O)H, -CO₂H, -(C=O)alkyl, -CO₂alkyl, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, carboxy, acyl, -C(=O)H, -C(=O)phenyl, -CO₂-alkyl, cycloalkyl, -(C=O)NH₂, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), -(C=O)N(alkyl)₂, -C(=O)-(CH₂)₁₋₂NH₂, -C(=O)-(CH₂)₁₋₂NH(alkyl), -C(=O)-(CH₂)₁₋₂N(alkyl)₂, -NH-CH₂-carboxy, -NH-CH₂-CO₂-alkyl, phenyl, benzyl, phenylethyl, or phenoxy. The group R_d may be selected from the same group as R_a, R_b and R_c but is not hydrogen. Alternatively, the groups R_a and R_b may together form a heterocyclo or heteroaryl ring. It should be understood that when a substituted alkyl group is substituted with an aryl, cycloalkyl, heteroaryl, or heterocyclo, such rings are as defined below and thus may have one to three substituents as set forth below in the definitions for these terms.

- When the term "alkyl" is used as a suffix following another specifically named group, *e.g.*, arylalkyl, heteroarylalkyl, the term defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, arylalkyl refers to an aryl bonded through an alkyl, or in other words, a substituted alkyl group having from 1 to 12 carbon atoms and at least one substituent that is aryl (*e.g.*, benzyl or biphenyl). "Lower arylalkyl" refers to substituted alkyl groups having 1 to 4 carbon atoms and at least one aryl substituent.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one double bond. Alkenyl groups of 2 to 6 carbon atoms and having one double bond are most preferred.

- 5 The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred. A substituted alkenyl or alkynyl will contain one, two, or three substituents as defined above for alkyl groups.

- 10 The term "alkylene" refers to bivalent straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, e.g., $\{-\text{CH}_2-\}_n$, wherein n is 1 to 12, preferably 1-8. Lower alkylene groups, that is, alkylene groups of 1 to 4 carbon atoms, are most preferred. The terms "alkenylene" and "alkynylene" refer to bivalent radicals of alkenyl and alkynyl groups, respectively, as defined above. Substituted alkylene, alkenylene, and alkynylene groups may have substituents as defined above for substituted alkyl groups.

- 15 The term "alkoxy" refers to the group OR_e wherein R_e is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocycle, or cycloalkyl. Thus, an alkoxy includes such groups as methoxy, phenoxy, benzyloxy, and so forth. The term "aryloxy" refers to the groups $\text{O}(\text{aryl})$ or $\text{O}(\text{heteraryl})$, wherein aryl and heteroaryl are as defined below.

- 20 The term "alkylthio" refers to an alkyl or substituted alkyl group as defined above bonded through one or more sulfur ($-\text{S}-$) atoms, e.g., $-\text{S}$ (alkyl) or $-\text{S}$ (alkyl- R_a).

The term "alkylamino" refers to an alkyl or substituted alkyl group as defined above bonded through one or more nitrogen ($-\text{NR}_g$) groups, wherein R_g is hydrogen, alkyl, substituted alkyl, or cycloalkyl.

- 25 The term "acyl" refers to an alkyl or substituted alkyl group as defined above bonded through one or more carbonyl $\{-\text{C}(=\text{O})-\}$ groups. When the term acyl is used in conjunction with another group, as in acylamino, this refers to the carbonyl group $\{-\text{C}(=\text{O})\}$ linked to the second group. Thus, acylamino refers to $-\text{C}(=\text{O})\text{NH}_2$, substituted

acylamino refers to the group $-C(=O)NRR$, and acylaryl refers to $-C(=O)(aryl)$ and $-C(=O)(naphthyl)$.

The term "aminoacyl" refers to the group $-N_fR_gC(=O)R_g$, wherein R_g is hydrogen, alkyl, or substituted alkyl, and R_f is as defined above for alkylamino groups.

5 The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "carboxy" when used alone refers to the group CO_2H . Carboxyalkyl refers to the group CO_2R , wherein R is alkyl or substituted alkyl.

The term "sulphonyl" refers to a sulphoxide group (*i.e.*, $-S(O)_{1-2-}$) linked to an organic radical including an alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, 10 or substituted alkynyl group, as defined above. The organic radical to which the sulphoxide group is attached may be monovalent (*e.g.*, $-SO_2$ -alkyl), or bivalent (*e.g.*, $-SO_2$ -alkylene, etc.)

The term "amidino" refers to the group $\begin{array}{c} NR_i \\ || \\ NR_h-C-R_j \end{array}$, and the term

"guanidino" refers to the group $\begin{array}{c} NR_i \\ || \\ NR_h-C-NHR_j \end{array}$, wherein for each of amidino and

15 guanidino R_h , R_i , and R_j may be hydrogen, alkyl, or substituted alkyl, or any two of R_h , R_i , and R_j may join to form a heterocyclo or heteroaryl ring with the other of R_h , R_i , and R_j comprising hydrogen, alkyl, or substituted alkyl.

The term "cycloalkyl" refers to substituted and unsubstituted monocyclic or bicyclic hydrocarbon groups of 3 to 9 carbon atoms which are, respectively, fully 20 saturated or partially unsaturated, including a fused aryl ring, for example, an indan. A cycloalkyl group may be substituted by one or more (such as one to three) substituents selected from alkyl, substituted alkyl, aminoalkyl, halogen, cyano, nitro, trifluoromethyl, hydroxy, alkoxy, alkylamino, sulphonyl, $-SO_2(aryl)$, $-CO_2H$, $-CO_2$ -alkyl, $-C(=O)H$, keto, $-C(=O)-(CH_2)_{1-2}NH_2$, $-C(=O)-(CH_2)_{1-2}NH(alkyl)$, $-C(=O)-(CH_2)_{1-2}N(alkyl)_2$, acyl, aryl, 25 heterocycle, heteroaryl, or another cycloalkyl ring of 3 to 7 carbon atoms. The term "cycloalkylene" refers to a cycloalkyl forming a link or spacer between two other groups, *i.e.*, a cycloalkylene is a cycloalkyl that is bonded to at least two other groups. The term

cycloalkyl includes saturated or partially unsaturated carbocyclic rings having a carbon-carbon bridge of three to four carbon atoms or having a benzene ring joined thereto.

- The term "aryl" refers to substituted and unsubstituted phenyl, 1-naphthyl and 2-naphthyl, with phenyl being preferred. The aryl may have zero, one, two or three substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, alkylthio, halo, hydroxy, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, sulphonyl, -SO₂(aryl), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, carboxy, acyl, -C(=O)H, -C(=O)phenyl, -CO₂-alkyl, cycloalkyl, -(C=O)NH₂, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), -(C=O)N(alkyl)₂, -NH-CH₂-carboxy, -NH-CH₂-CO₂-alkyl, -C(=O)-(CH₂)₁₋₂NH₂, -C(=O)-(CH₂)₁₋₂NH(alkyl), -C(=O)-(CH₂)₁₋₂N(alkyl)₂, phenyl, benzyl, phenylethyl, phenoxy, phenylthio, heterocyclo, heteroaryl, or a C₃₋₇cycloalkyl ring. The term "arylene" refers to an aryl as defined above forming a link or spacer between two other groups, *i.e.*, an arylene is an aryl that is bonded to at least two other groups.

- The term "carbocyclo" or "carbocyclic" refers to a cyclic group in which all ring atoms are carbon, including optionally-substituted cycloalkyl and aryl groups, as defined herein.

- The term "heterocyclo" or "heterocycle" refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may contain one, two or three substituents selected from the group consisting of halo, amino,

cyano, alkyl, substituted alkyl, trifluoromethyl, trifluoromethoxy, sulphonyl, -SO₂(aryl), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl, phenylethyl, phenoxy, phenylthio, carboxy, -CO₂-alkyl, cycloalkyl, -C(=O)H, acyl, -(C=O)NH₂, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), -(C=O)N(alkyl)₂, -NH-CH₂-carboxy, -NH-CH₂-CO₂-alkyl, -C(=O)-(CH₂)₁₋₂NH₂, -C(=O)-(CH₂)₁₋₂NH(alkyl), -C(=O)-(CH₂)₁₋₂N(alkyl)₂, heterocyclo, heteroaryl, a C₃₋₇cycloalkyl ring, keto, =N-OH, =N-O-lower alkyl, or a five or six membered ketal, i.e., 1,3-dioxolane or 1,3-dioxane. The heterocyclo ring may have a sulfur heteroatom that is substituted with one or more



oxygen (=O) atoms, as for example, in . The term "heterocyclene" refers to a heterocycle as defined above forming a link or spacer between two other groups.

Exemplary monocyclic groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain one, two or three substituents selected from

the group consisting of halo, amino, cyano, alkyl, substituted alkyl, trifluoromethyl, trifluoromethoxy, sulphonyl, $-\text{SO}_2(\text{aryl})$, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{N}(\text{alkyl})_2$, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl, phenylethyl, phenoxy, phenylthio, carboxy, $-\text{CO}_2\text{-alkyl}$, cycloalkyl, $-\text{C}(=\text{O})\text{H}$, acyl, $-(\text{C}=\text{O})\text{NH}_2$, $-(\text{C}=\text{O})\text{NH}(\text{alkyl})$, $-(\text{C}=\text{O})\text{NH}(\text{cycloalkyl})$, $-(\text{C}=\text{O})\text{N}(\text{alkyl})_2$, $-\text{NH}-\text{CH}_2\text{-carboxy}$, $-\text{NH}-\text{CH}_2\text{-CO}_2\text{-alkyl}$, $-\text{C}(=\text{O})-(\text{CH}_2)_{1-2}\text{NH}_2$, $-\text{C}(=\text{O})-(\text{CH}_2)_{1-2}\text{NH}(\text{alkyl})$, $-\text{C}(=\text{O})-(\text{CH}_2)_{1-2}\text{N}(\text{alkyl})_2$, heterocycloco, heteroaryl, or a C_{3-7} cycloalkyl ring. The heterocyclo ring may have a sulfur heteroatom.



that is substituted with one or more oxygen ($=\text{O}$) atoms, as for example, in . The term "heteroarylene" or "heterarylene" refers to a heteroaryl as defined above forming a link or spacer between two other groups, *i.e.*, it is a heteroaryl that is bonded to at least two other groups.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thieryl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl; phenanthridinyl, xanthenyl and the like.

When reference is made herein to a particularly-named substituted heterocyclic or heteroaryl group, such as "substituted azepinyl," "substituted homopiperazinyl," "substituted imidazolyl," "substituted piperazinyl," and so forth, the named ring may contain one or more (preferably one to three) substituents selected from halo, amino, cyano, nitro, alkyl, substituted alkyl (*e.g.*, trifluoromethyl), $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{N}(\text{alkyl})_2$, hydroxy, alkoxy, alkylthio, carboxy, $-\text{CO}_2\text{-alkyl}$, $-\text{C}(=\text{O})\text{H}$, acyl, $-(\text{C}=\text{O})\text{NH}_2$, $-(\text{C}=\text{O})\text{NH}(\text{alkyl})$, $-(\text{C}=\text{O})\text{NH}(\text{cycloalkyl})$, $-(\text{C}=\text{O})\text{N}(\text{alkyl})_2$, $-\text{NH}-\text{CH}_2\text{-carboxy}$, $-\text{NH}-\text{CH}_2-$

$\text{CO}_2\text{-alkyl}$, cycloalkyl, phenyl, benzyl, phenylethyl, phenoxy, phenylthio, heterocyclo, and heteroaryl. The term azetidinyl refers to an optionally-substituted four membered

ring having one nitrogen heteroatom, *i.e.*,  $(\text{R})_{0-3}$, wherein R can be any

substituent defined herein for heterocyclo groups and unless otherwise stated, the

- 5 azetidinyl ring can be attached to another group at any available carbon atom or at the nitrogen atom.

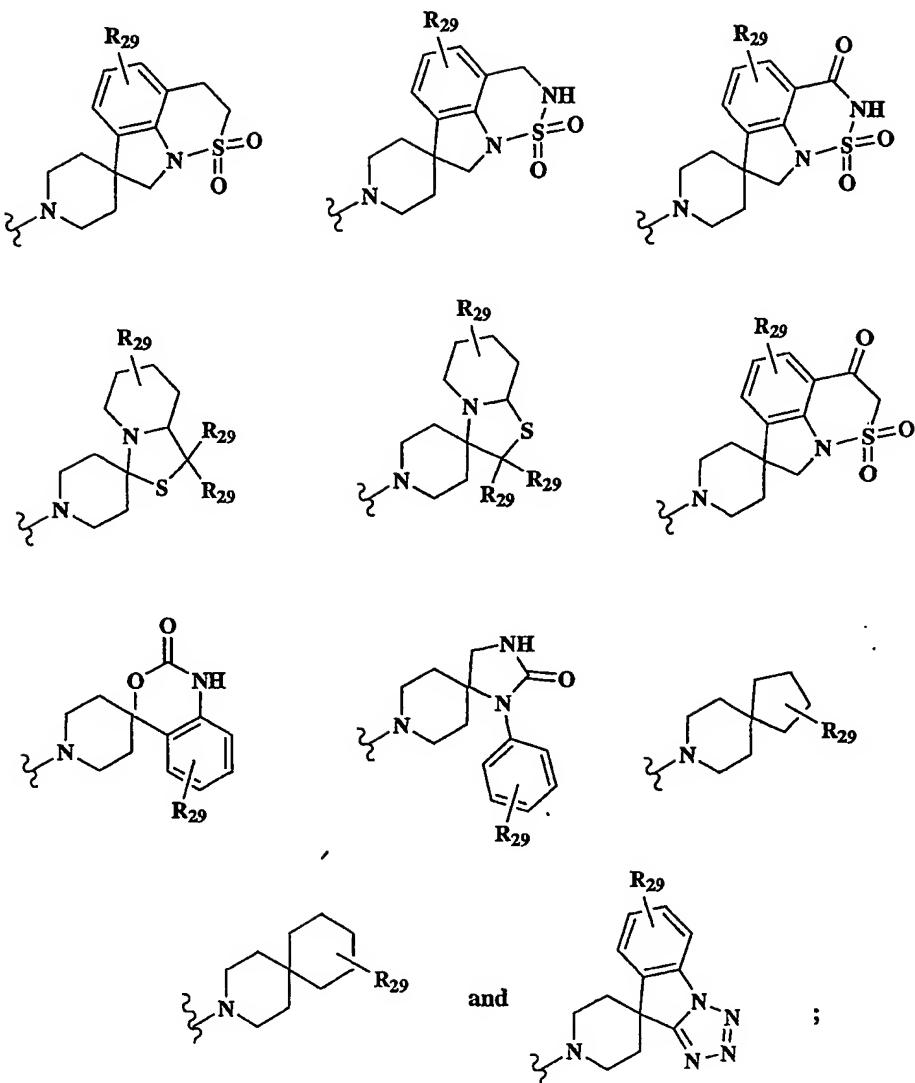
When reference is made to a particularly-named group having at least one heterocyclo, heteroaryl, or carbocyclic ring “joined” thereto, it is meant that two substituents attached to the same, adjacent, or non-adjacent atoms of the particularly-named group may join to form a second or third ring (*i.e.*, the further ring may be fused, bridged or attached in a spiro fashion.) Each ring of these bicyclic or tricyclic groups may be optionally substituted, wherein the substituents are selected from those recited above for cycloalkyl, aryl, heterocyclo and heteroaryl groups. Thus, the term “substituted imidazole” includes a monocyclic imidazole having one or more substituents selected

10 from halo, amino, cyano, nitro, alkyl, substituted alkyl (*e.g.*, trifluoromethyl), $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{N}(\text{alkyl})_2$, hydroxy, alkoxy, alkylthio, carboxy, $-\text{CO}_2\text{-alkyl}$, cycloalkyl, acyl, $-\text{C}(=\text{O})\text{H}$, $(\text{C}=\text{O})\text{NH}_2$, $-(\text{C}=\text{O})\text{NH}(\text{alkyl})$, $-(\text{C}=\text{O})\text{NH}(\text{cycloalkyl})$, $-(\text{C}=\text{O})\text{N}(\text{alkyl})_2$, $-\text{NH}-\text{CH}_2\text{-carboxy}$, $-\text{NH}-\text{CH}_2\text{-CO}_2\text{-alkyl}$, phenyl, benzyl, phenylethyl, phenoxy, phenylthio, heterocyclo, and heteroaryl. An imidazole having at least one ring joined

15 thereto may include an aryl-fused imidazole such as benzimidazole having one or more (preferably one to three substituents), to an heteroaryl-fused imidazole such as a pyridoimidazole having one or more (preferably one to three) substituents, and so forth.

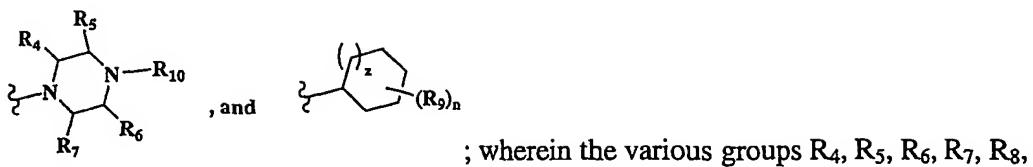
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Accordingly, the above definitions and optional substituents for cycloalkyl, heterocyclo, and heteroaryl groups include spirocyclic ring systems. To illustrate, in compounds of formula (I) above, R_8 and R_9 are recited as optionally forming a spirocyclic ring. Thus, when z is 1, R_8 and R_9 together with the piperidine to which they are attached may be selected from the following exemplary groups, among others:

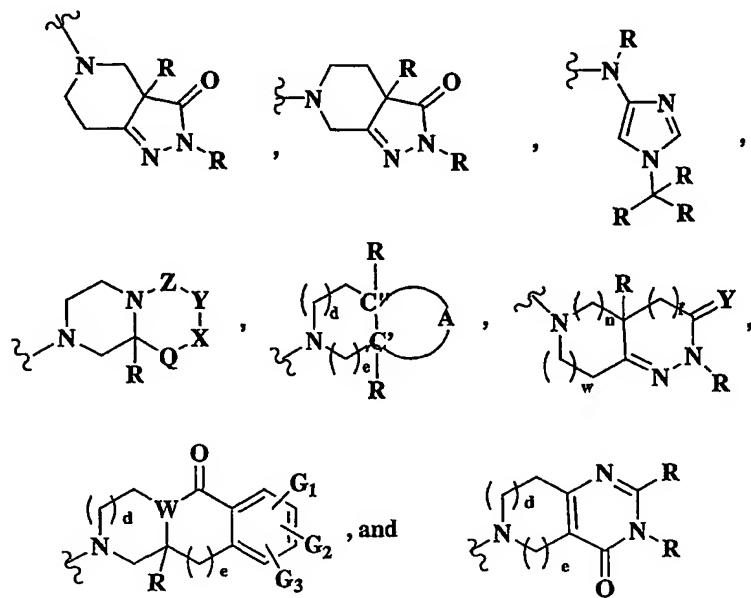


in which each R₂₉ group is hydrogen or selected from the above-recited substituents for aryl, cycloalkyl, heterocyclo and heteroaryl groups.

Additionally, one skilled in the field may make appropriate substitutions for the various groups of compounds of formula (I) herein, without departing from the spirit and scope of the invention. For example, it will be appreciated that in compounds of formula (I), the group E can be replaced with other groups, such as the groups E₂, E₃ and E₄ shown in International application Serial No. _____, incorporated herein, i.e., groups having the formula, -NR₁₁R₁₂,



R₉, R₁₀, R₁₁, and R₁₂ are as defined in that application. Additionally, one may appreciate that the group E as recited in compounds of formula (I) may be selected from, or replaced 5 with groups such as,



- 10 as defined in WO 02/00654 and WO 01/91752, wherein the various groups R, A, G₁₋₃, Q, W, X, Y, Z, d, e, f, n and w, may be selected from groups recited in WO 02/00654 and/or WO 01/91752, incorporated herein by reference.

Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

- 15 The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed

herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula I contains both a basic moiety, such as, but not limited to an amine or a pyridine or imidazole ring, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are 5 included within the term "salt(s)" as used herein. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also contemplated as within the scope of the invention, *e.g.*, they may be useful in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound of the formula I with 10 an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of formula I which contain a basic moiety, such as, but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those 15 formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with 20 hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), 25 sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

The compounds of formula I which contain an acidic moiety, such as, but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, 30 and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts

with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines [formed with N,N-bis(dehydroabietyl)ethylenediamine], N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

10 Prodrugs and solvates of the compounds of this invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, and/or a salt and/or solvate thereof. Solvates of the compounds of formula I are preferably hydrates.

15 Compounds of the formula I and salts thereof may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

20 All stereoisomers of the present compounds, such as those, for example, which may exist due to asymmetric carbons, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms, are contemplated and within the scope of this invention. Individual stereoisomers of the compounds of this invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the
25 IUPAC 1974 Recommendations.

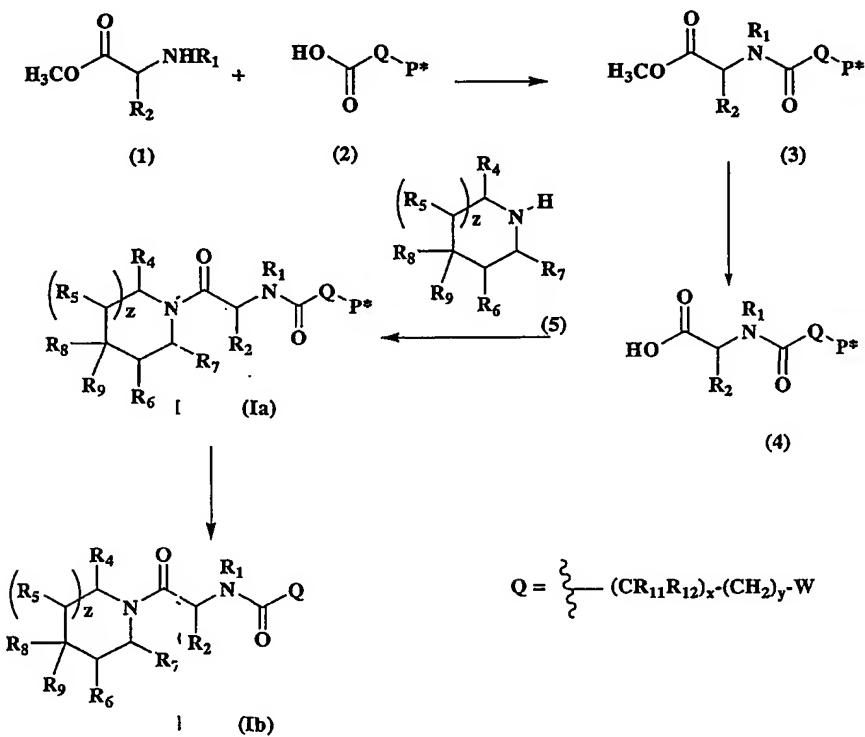
Methods of Preparation

The compounds of the present invention may be prepared by methods such as those illustrated in the following Schemes I to III. Starting materials are commercially

available or can be readily prepared by one of ordinary skill in the art using known methods. For all of the schemes and compounds, the designated groups such as E, W, R₈, R₉, etc., are as described above for a compound of formula I, unless otherwise indicated.

Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. High Speed Analoging (HSA) may be employed in the preparation of compounds, for example, where the intermediates possess a carboxylic acid or amino group.

10 **Scheme I**



Compounds of formula (Ib) can be prepared from compounds (Ia) [wherein P* is an amino protecting group, such as -Boc-, -CBZ-, -Fmoc-, which can be present in Q as in formula (Ia) or independently bonded to Q] via an appropriate amine deprotection process in an inert solvent at a temperature in the range -10°C to 100°C. The choice of

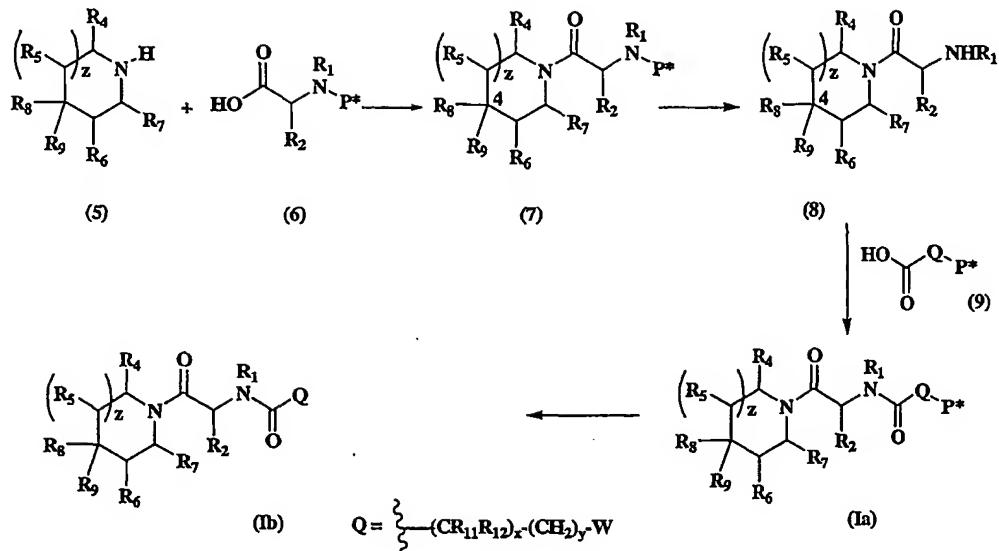
deprotection routes can be chosen by one of ordinary skill in the art. They include, but are not limited to TFA or hydrogen chloride acid for -Boc-, hydrogenation with an appropriate metal catalyst (such as Pd), for -CBZ-, or a base, such as NMM or DEA, for -Fmoc-. Inert solvents include, but are not limited to methylene dichloride, alcoholic solvents, THF, acetic acid, DMF, acetonitrile, and dioxane.

Compounds of formula (Ia) can be prepared by the coupling of compounds of formula (5) with compounds (4) using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH_2Cl_2 .

Compounds (4) can be prepared by the hydrolysis of compounds (3) using a hydroxide source. Exemplary hydroxide sources include NaOH or LiOH. Exemplary solvents include water, alcohols, and mixtures of ethers/water.

Compounds (3) can be prepared by the coupling of compounds (1) and (2) using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH_2Cl_2 .

Compounds (1), (2) and (3) are either commercially available or available by methods known to one of ordinary skill in the art.

Scheme II

Compounds of formula (Ib) can be prepared from compounds of formula (Ia) [wherein P* is an amino-protecting group as in Scheme I] via an appropriate amine deprotection process in an inert solvent at a temperature in the range from -10°C to 100°C. The choice of deprotection routes can be chosen by one of ordinary skill in the art. They include, but are not limited to TFA or hydrogen chloride acid for -Boc-, hydrogenation with an appropriate metal catalyst for -CBZ-, or a base, such as NMM or DEA, for -Fmoc-. Inert solvents include, but are not limited to methylene dichloride, alcoholic solvents, THF, acetic acid, DMF, acetonitrile, and dioxane.

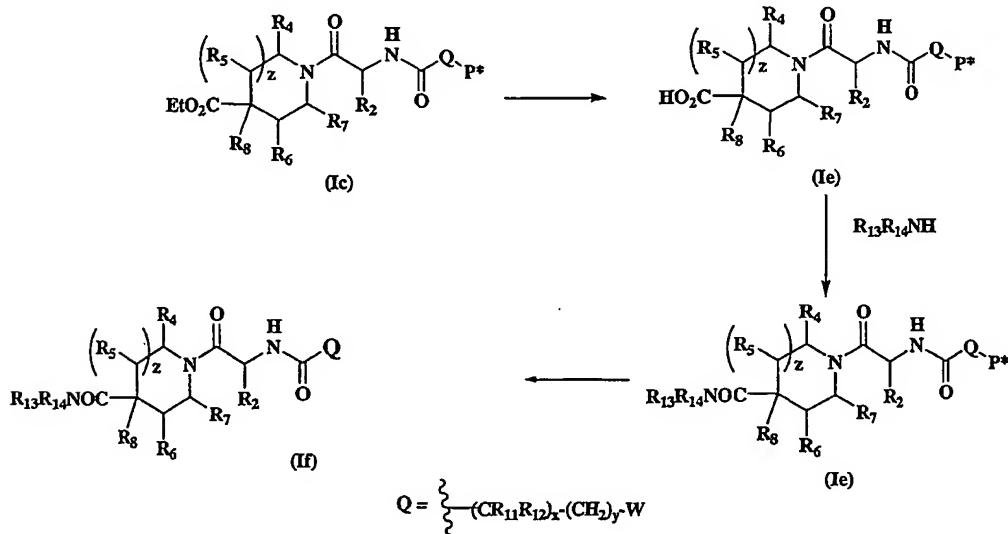
Compounds of formula (Ia) can be prepared by the coupling of compounds (8) and (9) using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH₂Cl₂.

Compounds (8) [wherein P* is an amino-protecting group as above] can be prepared from compounds (7) via an appropriate amine deprotection process in an inert solvent at temperatures ranging from -10°C to 100 °C. The choice of deprotection routes can be chosen by one of ordinary skill in the art and include those referenced above in 5 Scheme I for -Boc-, -CBZ-, and -Fmoc-. Inert solvents include, but are not limited to methylene dichloride, alcoholic solvents, THF, acetic acid, DMF, acetonitrile, and dioxane.

Compounds (7) can be prepared by the coupling of compounds (5) and (6) using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary 10 carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH₂Cl₂.

Compounds (5) and (6) are either commercially available or available by methods 15 known to one of ordinary skill in the art.

Scheme III



Compounds of formula (If) can be prepared from compounds of formula (Ie) [wherein P* is an amino protecting group as in Scheme I] via an appropriate amine deprotection process chosen by one of ordinary skill in the art, such as described above in 5 Schemes I and II.

Compounds of formula (Ie) can be prepared by the coupling of compounds of formula (Id) with amines of the formula R₁₃R₁₄NH using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentafluorophenol 10 trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH₂Cl₂.

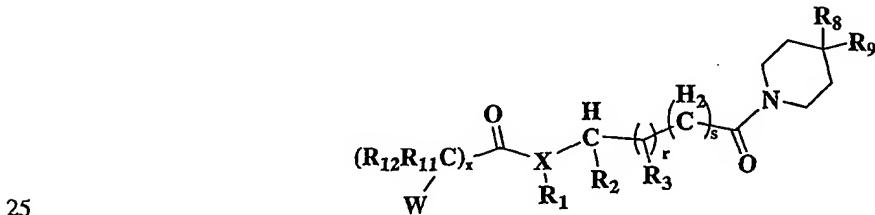
Compounds of formula (Id) can be prepared by the hydrolysis of compounds of formula (Ic) using a hydroxide source. Exemplary hydroxide sources include NaOH or 15 LiOH. Exemplary solvents include water, alcohols, and mixtures of ethers/water.

Amines of the formula R₁₃R₁₄NH are either commercially available or available by methods known to one of ordinary skill in the art. Compounds of formula (Ic) can be prepared as described above in Schemes I and II.

All documents cited in the present specification are incorporated herein by 20 reference in their entirety.

Preferred Compounds

Preferred compounds are those according to formula (I) having the formula,



and pharmaceutically-acceptable salts, hydrates and prodrug thereof,

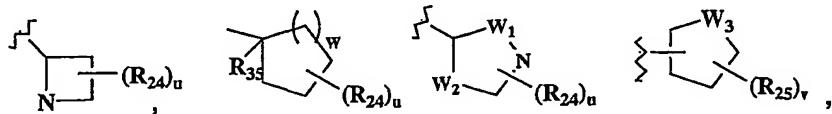
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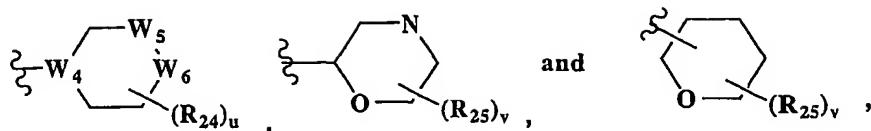
X is N or CH;

- 5 R₁ is hydrogen or C₁₋₆alkyl or is joined together with R₂ or R₃ to form a monocyclic or bicyclic heteroaryl or heterocycle;
- R₂ is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo, or C₁₋₆alkyl or C₂₋₆alkenyl optionally substituted with one to three of hydroxy, halogen, aryl, cycloalkyl, heteroaryl, and/or heterocyclo; or R₁ is joined together with R₂ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;
- 10 R₃ is hydrogen or C₁₋₆alkyl or is joined together with R₂ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;
- R₈ and R₉ are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl,
- 15 R₁₁ and R₁₂ are selected independently of each other from hydrogen, alkyl, halogen, hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl, cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, or R₁₁ and R₁₂, when attached to the same carbon atom, may join to form a spirocycloalkyl ring;

W is selected from:

- 20 1) -NR₁₆R₁₇, -NR₁₆C(=O)R₂₂, or -NR₁₆CO₂R₂₂; or
- 2) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said heteroaryl and heterocyclo groups may be optionally substituted with one to three R₃₆, and may have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused thereto; or
- 25 3) a carbocyclic, heterocyclic, or heteroaryl ring selected from:





in which W_1 and W_2 are NH, CH₂, O or S, W_3 is O or S, W_4 is N or CH, and W_5 and W_6 are NH or CH₂, wherein when W_1 , W_2 , W_5 and W_6 are NH or CH₂, said groups are optionally substituted with R_{24} ;

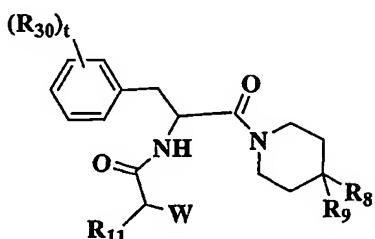
- 5 R_{16} and R_{17} are hydrogen, C₁₋₈alkyl or (CH₂)_jJ,
wherein J is selected from aryl, heteroaryl, heterocyclo, or cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R_{16} and/or R_{17} are optionally substituted with up to three R_{32} ;

R_{22} is selected from C₁₋₆alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl,
10 phenyl, pyrrolylalkyl, piperidinyl, and piperidinylalkyl, wherein R_{22} in turn is optionally substituted with one to two C₁₋₄alkyl and/or -CO₂(C₁₋₄alkyl); and
 R_{24} and R_{25} at each occurrence are attached to any available carbon or nitrogen atom of W and at each occurrence are selected from hydrogen, C₁₋₆alkyl, halogen, substituted C₁₋₆alkyl, amino, alkylamino, hydroxy, C₁₋₄alkoxy, -C(=O)R₂₆, -CO₂R₂₆,
15 -SO₂R₂₆, -OR₂₆, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R_{25} attached to two adjacent nitrogen or carbon atoms may join to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R_{24} or two R_{25} when attached to the same carbon atom may form keto (=O);

- R_{26} is alkyl, phenyl, benzyl, or aminoalkyl;
20 R_{32} is selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, halogen, nitro, phenyl, benzyl, phenoxy, benzyloxy, -C(=O)phenyl, amino, alkylamino, and aminoalkyl, wherein when R_{32} includes a phenyl group said phenyl group in turn is optionally substituted with one to two of halogen, nitro, cyano, C₁₋₄ alkyl, and/or C₁₋₄ alkoxy;
25 R_{35} and R_{36} at each occurrence are selected from C₁₋₆alkyl, halogen, substituted C₁₋₆alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, acyl, carboxyalkyl, sulfonyl, aryl, heteroaryl, heterocyclo, and cycloalkyl;
 j is selected from 0, 1, 2 and 3;

- r* is 0 or 1;
s is 0 or 1;
u and *v* are 0, 1, or 2;
w is 0, 1, or 2; and
5 *x* is 0, 1, 2, 3, or 4.

More preferred are compounds according to the formula,



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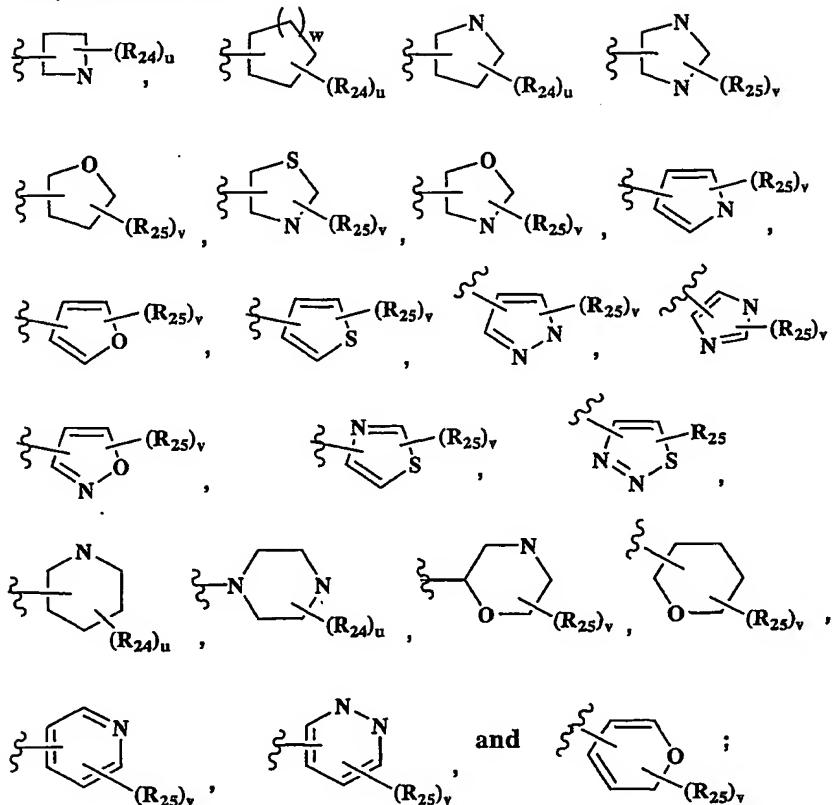
in which

R_8 and R_9 are selected independently from hydrogen, alkyl, substituted alkyl, heterocyclo, heteroaryl, cycloalkyl, and aryl;

- 15 R_{11} is hydrogen, C_{1-6} alkyl, or C_{1-6} alkyl substituted with up to two of hydroxy, alkoxy, amino, alkylamino, imidazolyl, pyrazolyl, phenyl, naphthyl, pyridinyl, indolyl, pyrimidyl, furyl, thiazolyl, and thienyl, wherein when said ringed substituents in turn are optionally substituted,

W is a) $-\text{NR}_{16}\text{R}_{17}$, $-\text{NHC}(=\text{O})\text{R}_{22}$, or $-\text{NHCO}_2\text{alkyl}$, or

b) a ring selected from:



and where at least one of x and/or y is at least 1, W may be $\overline{N} \longrightarrow (R_{25})_u$, wherein B is N, O or S;

R₁₆ and R₁₇ are independently selected from hydrogen, C₁₋₈alkyl, and (CH₂)_q-J, wherein J is selected from naphthyl, furanyl, indolyl, imidazolyl, pyrimidinyl, benzothiophenyl, pyridinyl, pyrrolyl, pyrrolidinyl, thiophenyl, and C₃₋₇cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R₁₆ and/or R₁₇ are optionally substituted:

R₂₂ is selected from C₁₋₆alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrrolylalkyl, piperidinyl, and piperidinylalkyl, wherein R₂₂ in turn is optionally substituted with one to two C₁₋₄alkyl and/or -CO₂(C₁₋₄alkyl);

R_{24} is selected from keto (=O), C_{1-6} alkyl, halogen, amino, aminoalkyl, alkylamino, hydroxy, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, $-C(=O)$ alkyl, $-C(=O)$ aminoalkyl, $-C(=O)$ phenyl, $-C(=O)$ benzyl, $-CO_2$ alkyl, $-CO_2$ phenyl, $-CO_2$ benzyl, $-SO_2$ alkyl, $-SO_2$ aminoalkyl, $-SO_2$ phenyl, $-SO_2$ benzyl, phenyl, benzyl, phenoxy, benzyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl, and each R_{24} in turn is optionally substituted with one to two R_{31} ;

R_{25} at each occurrence is attached to any available carbon or nitrogen atom of W and is

selected from C_{1-6} alkyl, halogen, amino, aminoalkyl, alkylamino, hydroxy, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, $-C(=O)$ alkyl, $-C(=O)$ aminoalkyl, $-C(=O)$ phenyl,

$-C(=O)$ benzyl, $-CO_2$ alkyl, $-CO_2$ phenyl, $-CO_2$ benzyl, $-SO_2$ alkyl, $-SO_2$ aminoalkyl, $-SO_2$ phenyl, $-SO_2$ benzyl, phenyl, benzyl, phenoxy, benzyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl, and/or two R_{25} when attached to adjacent carbon and/or nitrogen atoms may be taken together to form a fused benzo or pyrazolyl ring, and/or two R_{25} when attached to the same carbon atom (in the case of a non-aromatic ring) may form

keto (=O), and each R_{25} in turn is optionally substituted with up to two R_{31} ;

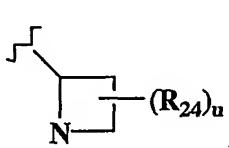
R_{30} is selected from C_{1-4} alkyl, hydroxy, alkoxy, halogen, nitro, cyano, amino, alkylamino, phenyl, and $-C(=O)$ phenyl;

R_{31} is selected from halogen, trifluoromethyl, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

w is selected from 0, 1, or 2;

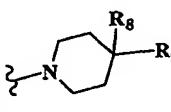
u and v are selected from 0, 1, and 2; and

t is 0, 1 or 2.

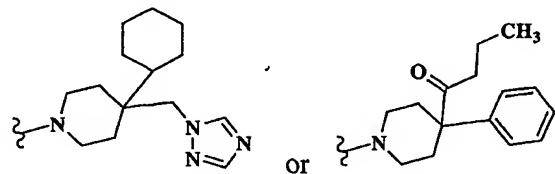
In compounds of formula (I), preferably W is  $, -NR_{16}R_{17}$, or $NR_{16}C(=O)R_{22}$, more preferably W is NH_2 , $NH(alkyl)$, $N(alkyl)_2$, or $N(CH_2)_{1-3}-J$, wherein J is heterocyclo, heteroaryl, aryl or cycloalkyl, or wherein R_{24} is hydrogen or lower alkyl

In compounds of formula (I), preferably R₁₂ is hydrogen or lower alkyl, and R₁₁ is preferably alkyl, heterocycloalkyl, heteroarylalkyl, or cycloalkylalkyl, more preferably imidazolylalkyl.

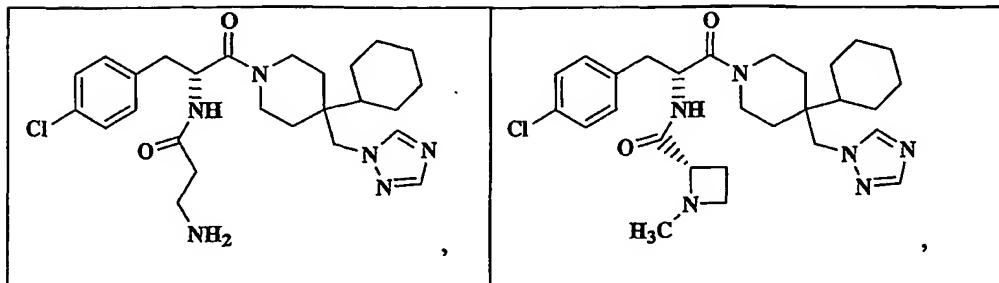
- 5 In compounds of formula (I), preferably R₂ is arylalkyl, arylalkenyl, or heteroarylalkyl, more preferably benzyl optionally substituted in the para position with lower alkyl, halogen, hydroxy, methoxy, cyano, trifluoromethyl, trifluoromethoxy, or nitro, more preferably chloro or fluoro.
- 10 In compounds of formula (I), preferably X is N, R₁ is hydrogen or lower alkyl, and r and s are preferably 0.

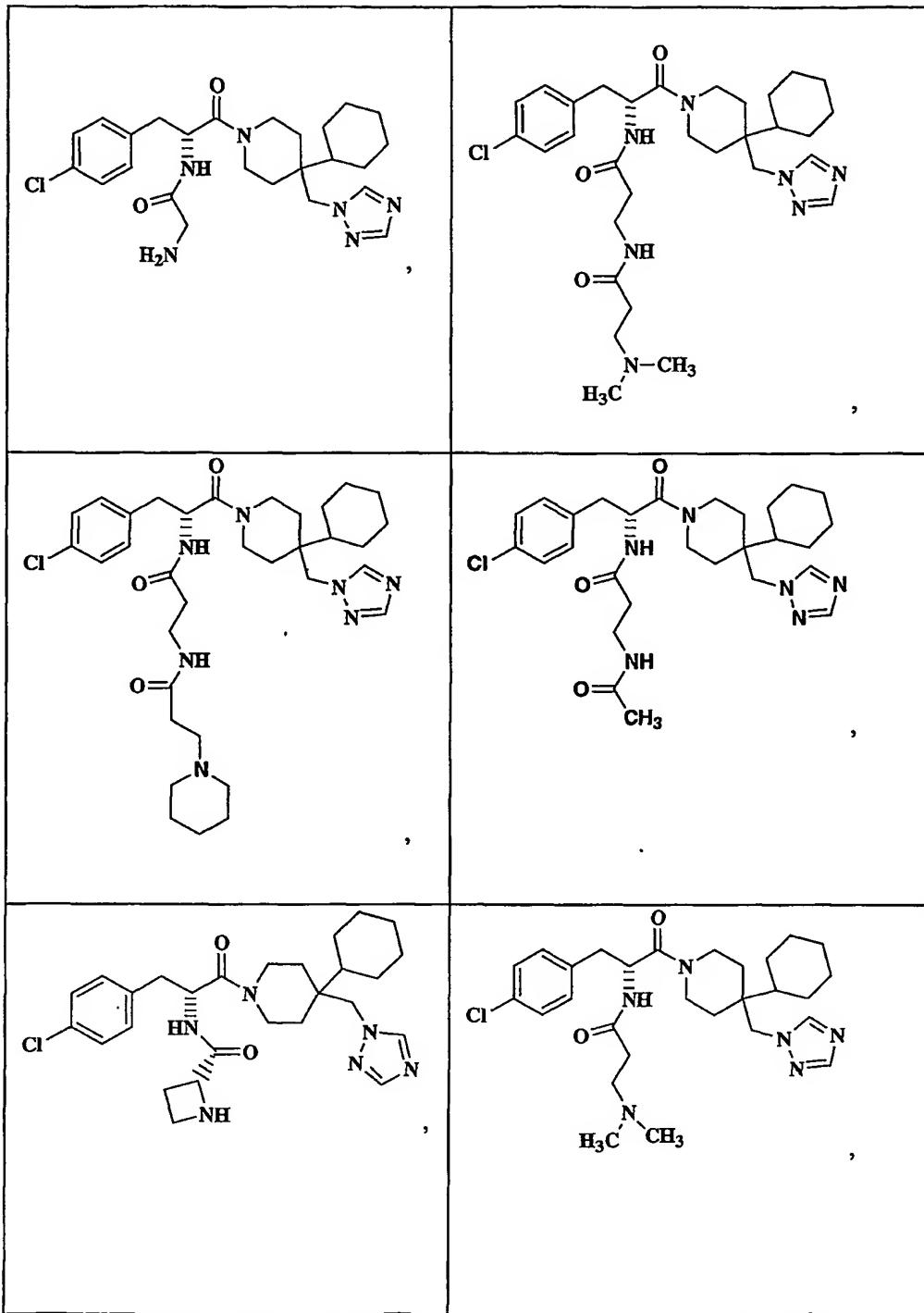
In compounds of formula (I), preferably E is  , wherein

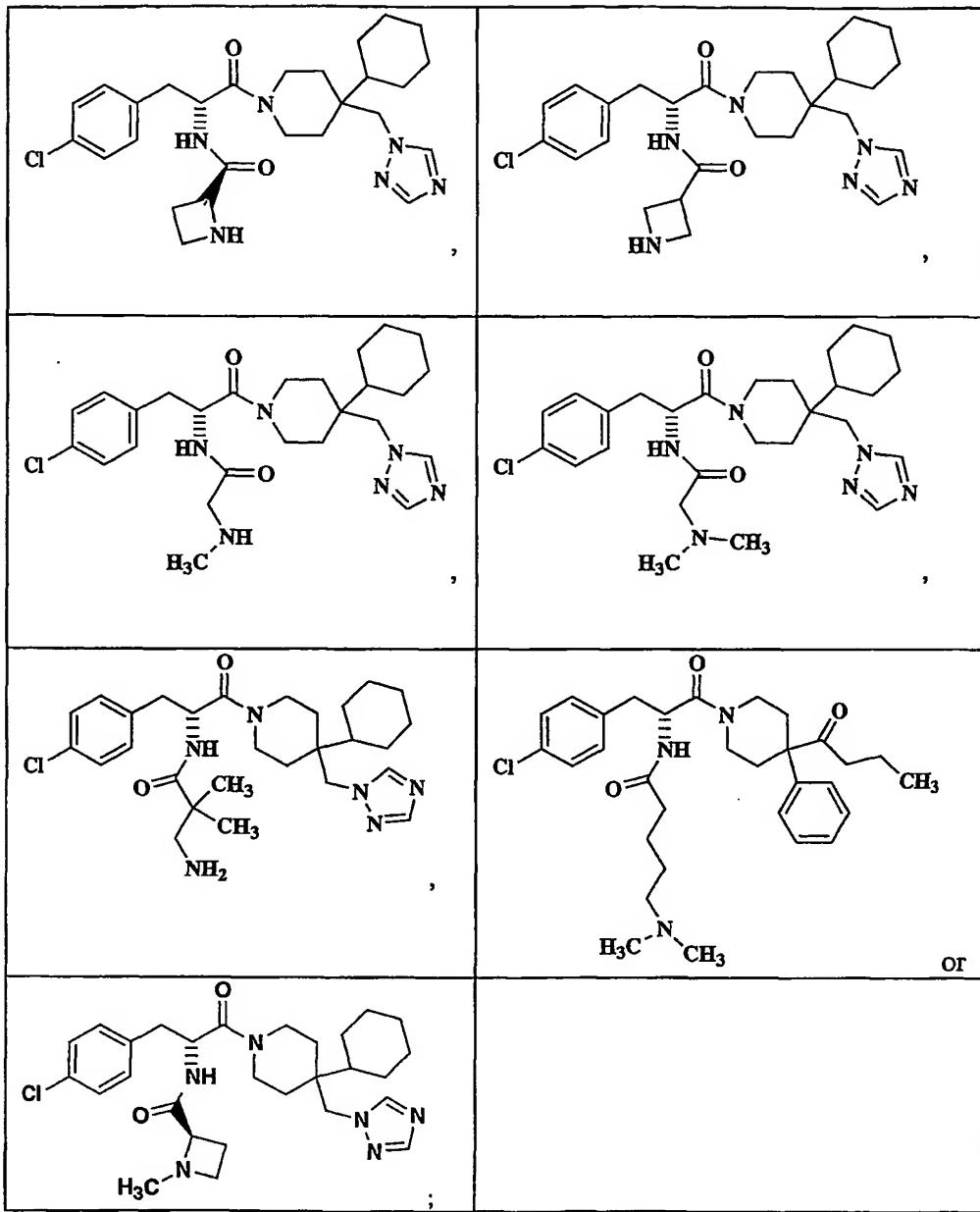
R₈ and R₉ are selected independently from hydrogen, alkyl, -(CH₂)_j-C(=O)alkyl, -(CH₂)_j-phenyl, -(CH₂)_j-naphthyl, -(CH₂)_j-C₄₋₇cycloalkyl, -(CH₂)_j-heterocyclo, and -(CH₂)_j-heteroaryl, or R₈ and R₉ together form a spirocycloalkyl or spiroheterocyclic ring; and j is selected from 0, 1, 2 and 3. More preferably, E is



20 Also preferred are compounds having the formulae:







and pharmaceutically-acceptable salts, hydrates and prodrugs thereof.

Utility

The inventive compounds are modulators of the melanocortin receptors MC-1R, MC-3R, MC-4R, and/or MC-5R. The compounds are useful in treating a wide range of conditions responsive to regulation of the melanocortin receptors, including inflammatory and immune diseases, cardiovascular diseases, skin conditions, neurodegenerative

5 conditions, sexual dysfunction, bodyweight disorders, and cancer. Certain compounds according to the invention have selective affinity for one melanocortin receptor relative to the other melanocortin receptors and thus are particularly useful for treating those diseases responsive to regulation of that receptor. For example, certain compounds have high selectivity for binding to MC-1R relative to MC-3R, MC-4R, and MC-5R, and those

10 compounds are particularly useful in treating inflammatory or immune conditions.

Certain other compounds according to the invention have high selective affinity for MC-4R and are particularly useful in treating bodyweight and/or neurodegenerative disorders.

As used herein, the term "treating" or "treatment" refers to prophylaxis measures designed to inhibit or delay the onset of the disease or disorder and to responsive

15 measures to alleviate, ameliorate, lessen, or cure the disease or disorder and/or its symptoms.

Compounds of the invention may be used to treat inflammation, particularly inflammation characterized by the activation of NF- κ B and/or release of inflammatory cytokines. The compounds can be immunomodulators and have multiple effects on cells

20 of the immune system. The compounds may be used to increase the levels of cAMP in cells (with resultant anti-inflammatory effects), decrease levels of the pro-inflammatory messenger nitric oxide, decrease chemotactic ability, and alter the expression of immune-related genes for such agents as cytokines, adhesion molecules, and nitric oxide synthase.

In view of their effects on inhibiting NF- κ B activity and suppressing cytokine

25 accumulation, the compounds will be useful in treating consequences of many diseases associated with chronic and acute inflammation and immune-modulation. Such diseases include, but are not limited to, inflammatory bowel disease, irritable bowel syndrome, gall bladder disease, Crohn's disease, rheumatoid arthritis, osteoarthritis, osteoporosis, traumatic arthritis, rubella arthritis, muscle degeneration, pancreatitis (acute or chronic),

30 psoriasis, glomerulonephritis, serum sickness, lupus (systemic lupus erythematosus),

urticaria, scleroderma, schleroderma, chronic thyroiditis, Grave's disease, dermatitis (contact or atopic), dermatomyositis, alopecia, atopic eczemas, ichthyosis, fever, sepsis, migraine, cluster headaches, Alzheimer's Disease, Parkinson's disease, Creutzfeldt-Jacob disease, multiple sclerosis, tuberculosis, dementia, and transplant or graft-host rejections
5 (e.g., kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts and heterografts, etc.); The compounds may also be used to treat respiratory allergies and diseases including asthma, acute respiratory distress syndrome, hayfever, allergic rhinitis, and chronic obstructive pulmonary disease; and inflammatory disorders of the central nervous system, including HIV encephalitis,
10 cerebral malaria, meningitis, and ataxia telangiectasis. Additionally, the compounds may be useful in treating pain, e.g., post-operative pain, neuromuscular pain, headache, pain cause by cancer, dental pain, and arthritis pain.

In view of their activity in inhibiting NF- κ B activity, the compounds may be used to treat viral and autoimmune diseases including herpes simplex type 1 (HSV-1), herpes
15 simplex type 2 (HSV-2), cytomegalovirus, Epstein-Barr, human immunodeficiency virus (HIV), Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease (also known as autoimmune
polyglandular syndrome), chronic active hepatitis or acute hepatitis infection (including hepatitis A, hepatitis B, and hepatitis C), autoimmune gastritis, autoimmune hemolytic
20 anemia, and autoimmune neutropenia. The compounds of the invention may also be used to treat fungal infections such as mycosis fungoides.

In addition, the compounds of this invention are useful in treating diseases of the cardiovascular system including those diseases in which inflammation is an underlying component. These diseases include but are not limited to atherosclerosis,
25 transplant atherosclerosis, peripheral vascular disease, inflammatory vascular disease, intermittent claudication, restenosis, cerebrovascular stroke, transient ischemic attack, myocardial ischemia and myocardial infarction. The compounds also may be used to treat hypertension, hyperlipidemia, coronary artery disease, unstable angina, thrombosis, thrombin-induced platelet aggregation, and/or consequences occurring from thrombosis
30 and/or the formation of atherosclerotic plaques.

Additionally, the compounds may be useful to treat stroke and other ischemic brain diseases and/or neurodegeneration associated therewith, and the neurodegeneration of, and consequences of, traumatic brain injury.

In view of their ability to act as immunomodulators in the skin and affect the
5 production of melanin in the skin, these compounds are useful in altering pigmentation in the skin and may be used as photoprotective agents including agents for preventing, treating, or ameliorating sunburn. The compounds also may be used in treating acne, vitiligo, alopecia areata, photosensitivity disorders, albinism, and porphyria.
10 Additionally, the compounds are useful to promote cosmetic as well as therapeutic tanning.

The compounds of the invention may also be used to treat neurodegenerative disorders including depression, anxiety, compulsion (obsessive-compulsive disorder), neuroses, psychosis, insomnia/sleep disorder, sleep apnea, and drug or substance abuse.

The compounds of the invention may be used to treat male or female sexual
15 dysfunction. Male sexual dysfunction includes impotence, loss of libido, and erectile dysfunction (including but not limited to an inability to achieve or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve an orgasm). Female sexual dysfunction may include sexual arousal disorder or disorders relating to desire, sexual receptivity, orgasm, and/or disturbances in trigger points of sexual function.
20 Female sexual dysfunction may also include sexual pain, premature labor, dysmenorrhea, excessive menstruation, and endometriosis.

The compounds of the invention may also be used to treat bodyweight disorders including but not limited to obesity and anorexia (e.g., by altering appetite, metabolic rate, fat intake or carbohydrate craving); and diabetes mellitus (by enhancing glucose
25 tolerance and/or decreasing insulin resistance).

The compounds also may be used to treat cancer, more particularly, cancer of the lung, prostate, colon, breast, ovaries, and bone, or angiogenic disorders including the formation or growth of solid tumors.

The compounds of the invention may also be used to treat veterinary disease such as veterinary viral infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus.

The term "melanocortin-receptor associated condition" when used herein refers 5 to each of the above-referenced conditions, disorders, or diseases that may be treated by agonizing or antagonizing a melanocortin receptor, inhibiting NF- κ B activity and/or suppressing cytokine accumulation as if each of these conditions, disorders and diseases were set forth herein at length.

The inventive compounds may be used alone or in combination with each other 10 and/or other therapeutic agents such as anti-inflammatory drugs, , antibiotics, , anti-viral agents, anti-fungal agents, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents or appetite suppressants, growth promoting agents (including growth hormone secretagogues), anti-anxiety agents, anti-depressants, anti-hypertensive agents, cholesterol/lipid lowering agents, bone resorption inhibitors, and anti-tumor agents 15 including antiproliferative agents , or cytotoxic drugs. ,

Examples of suitable other anti-inflammatory agents with which the inventive compounds may be used include aspirin, non-steroidal antiinflammatory drugs (NSAIDs) (such as ibuprofen and naproxin), TNF- α inhibitors (such as tenidap and rapamycin or derivatives thereof), or TNF- α antagonists (*e.g.*, infliximab, OR1384), prednisone, 20 dexamethasone, Enbrel®, cyclooxygenase inhibitors (*i.e.*, COX-1 and/or COX-2 inhibitors such as Naproxen®, Celebrex®, or Vioxx®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®), integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, prostaglandin synthesis inhibitors, budesonide, 25 clofazimine, CNI-1493, CD4 antagonists (*e.g.*, priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, therapies for the treatment of irritable bowel syndrome (*e.g.*, Zelmac® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1), or other NF- κ B inhibitors, such as corticosteroids, calphostin, CSAIDs, 4-substituted imidazo [1,2-A]quinoxalines as

disclosed in US Pat. No. 4,200,750; Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; and nuclear translocation inhibitors, such as deoxyspergualin (DSG). To treat pain such as migraine and other headaches, the inventive compounds may be used in combination with aspirin, NSAIDs, or with 5-HT_{ID}

5 receptor agonists such as sumatriptan, eletriptan or rizatriptan.

Examples of suitable other antibiotics with which the inventive compounds may be used include β -lactams (e.g., penicillins, cephalosporins and carbopenams); β -lactam and lactamase inhibitors (e.g., augmentin); aminoglycosides (e.g., tobramycin and streptomycin); macrolides (e.g., erythromycin and azithromycin); quinolones (e.g., cipro

10 and tequin); peptides and depeptides (e.g. vancomycin, synercid and daptomycin) metabolite-based anti-biotics (e.g., sulfonamides and trimethoprim); polyring systems (e.g., tetracyclines and rifampins); protein synthesis inhibitors (e.g., zyvox, chlorophenicol, clindamycin, etc.); and nitro-class antibiotics (e.g., nitrofurans and nitroimidazoles).

Examples of suitable other antifungal agents with which the inventive compounds may be used include fungal cell wall inhibitors (e.g., candidas), azoles (e.g., fluconazole and vericonazole), and membrane disruptors (e.g., amphotericin B).

Examples of suitable other antiviral agents for use with the inventive compounds include nucleoside-based inhibitors, protease-based inhibitors, and viral-assembly inhibitors.

20 Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g., metformin or phenformin), glucosidase inhibitors (e.g., acarbose or miglitol), insulins (including insulin secretagogues, sensitizers or mimetics), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, gliclazide, chlorpropamide and glipizide),

25 biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), glucagon-like peptide-1 (GLP-1), dipeptidyl peptidase IV (DP4) inhibitors, Alistat®, Meridia®, and Zenacol®.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment, raloxifene, calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-1 inhibitors.

5 Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in
10 U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), a serotonin, adrenergic (and dopamine) reuptake inhibitor, such as sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), other thyroid receptor beta drugs, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425
15 (KaroBio), and/or an anorectic agent (such as dexamphetamine, phentermine, phenylpropanolamine or mazindol). Additionally, the inventive compounds may be used with an α -glucosidase inhibitor, an MHC-CoA reductase inhibitor, a sequestrant cholestorol lowering agent, a β 3 adrenergic receptor agonist, a neuropeptide Y antagonist, or an α 2-adrenergic receptor antagonist.

20 A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators.

25 A further use of the compounds of this invention is in combination with steriodal or non-steroidal progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include benzodiazepines, diazepam, lorazepam, buspirone (Serzone®), oxazepam, and hydroxyzine pamoate, or dopamine receptor agonists.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

- In treating skin disorders or diseases as described above, the compounds may be
5 used alone or in combination with a retinoid, such as tretinoin, or a vitamin D analog.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (*e.g.*, chlorothiazide, hydrochlorothiazide, flumethiazide,
10 hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynahen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, and spironolactone), renin inhibitors, ACE inhibitors (*e.g.*, captopril, Vanlev®, pravachol, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor
15 antagonists (*e.g.*, losartan, irbesartan, valsartan), ET receptor antagonists (*e.g.*, sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (*e.g.*, compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors)
(*e.g.*, omapatrilat and gemopatrilat), nitrates, and cardiac glycosides (*e.g.*, digitalis and
20 ouabain).

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipoxygenase inhibitors, an ileal Na⁺/bile acid cotransporter inhibitor,
25 cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (*e.g.*, CP-529414).

In addition, the compounds may be used with other agents to increase the levels of cAMP or cGMP in cells for a therapeutic benefit. For example, applicants have discovered that MC-1R agonists including the compounds of the invention have

advantageous effects when used in combination with phosphodiesterase inhibitors, including PDE1 inhibitors (such as those described in Journal of Medicinal Chemistry, Vol. 40, pp. 2196-2210 [1997]), PDE2 inhibitors, PDE3 inhibitors (such as revizinone, pimobendan, or olprinone), PDE4 inhibitors (such as rolipram, cilomilast, or piclamilast), 5 and PDE7 inhibitors. The compounds of this invention also may be used in combination with PDE5 inhibitors such as sildenafil, sildenafil citrate, (*e.g.*, when treating sexual dysfunction) or IC-351.

The combination of the inventive compounds with other therapeutic agents may prove to have additive and synergistic effects. The combination may be advantageous to 10 increase the efficacy of the administration or decrease the dosage to reduce possible side-effects. The compounds of formula I may be administered by any means suitable for the condition to be treated. The compounds may be delivered orally such as in the form of tablets, capsules, granules, powders, or with liquid formulations including syrups; sublingually; buccally; transdermally; parenterally such as by subcutaneous, intravenous, 15 intramuscular, or intrasternal injection or infusion (*e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended 20 release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium 25 alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may be orally 30 delivered by sublingual and/or buccal administration, *e.g.*, with molded, compressed, or

freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include
10 solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable
15 diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic
20 glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art. The specific dose level and frequency of dosage for any particular subject may vary and will depend upon a variety of factors, including the
25 activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. An exemplary effective amount of compounds of formula I may be within the dosage range of about 0.1 to about 100 mg/kg, preferably

about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like, subject to melanocortin-receptor associated conditions.

5 Each of the inventive compounds exemplified herein has been tested and shown activity at a measurable level for modulating a melanocortin receptor, according to an assay described below and/or an assay known in the field, such as, for example, assays described in WO 00/74679 A1 and WO 01/91752.

10 **Assays**

MC1R

HBL cells, a human melanoma cell line licensed from Prof. G. Ghanem (Lab. of Oncology & Exp. Surgery, Free University of Brussels, Brussels, Belgium) were used as a source of the human MC-1R. cAMP was measured using the cAMP SPA Direct Screening Assay System from Amersham (RPA 559). 20,000 HBL cells were plated into each well of a half-area 96 well white plate and were used between 16-48 hours after plating. Cells were incubated at 37°C for 15 minutes in 25 uM IBMX to inhibit phosphodiesterase activity. As per kit instructions, Assay Buffer Concentrate was diluted 1 to 50 with dH₂O to prepare Assay Buffer (50 mM acetate buffer containing 0.01% sodium azide). Vials containing rabbit anti-succinyl cAMP serum and the tracer, adenosine 3',5'-cyclic phosphoric acid 2'-O-succinyl-3-[¹²⁵I] iodotyrosine methyl ester, were resuspended with 7.5 ml Assay Buffer. SPA anti-rabbit reagent (donkey anti-rabbit IgG coupled to SPA PVT beads) was resuspended with 15 ml Assay Buffer. All reagents were stored at 4°C after reconstitution. Melanocortin ligands or compounds were prepared in DMSO and added to the IBMX-treated cells as 100X concentrated stocks. 50 nM α-MSH was used for the maximum response and 1 ul DMSO was included in the negative control wells. The final concentration of DMSO was 1% in all the samples. After 15-30 minutes of stimulation, the reaction was terminated by the aspiration of the contents of the well followed by addition of 15 ul Assay Buffer containing 0.1 N HCl.

Plates were kept at room temperature for at least 30 minutes to effect extraction of cAMP. Antiserum, Tracer, and SPA anti-rabbit reagent solutions were mixed 1:1:1 just prior to use. 15 ul of SPA reagent mixture was dispensed into each well and plates were incubated at room temperature for a minimum of 5 hours. Plates were subsequently 5 counted for 6 minutes per sample in a TopCount scintillation reader with background subtraction. Data was analyzed in relation to a cAMP standard curve.

MC-4R

A. Binding Assay.

The membrane binding assay may be used to identify competitive inhibitors of 10 [125 I]NDP- α -MSH binding to cloned human MC4R expressed in Hi5 insect cells infected by a baculovirus/human MC4R receptor construct.

Hi5 cells are grown in suspension in Express Five SFM Insect Cell Media (Gibco, Cat. No. 10486-025) at 27°C with constant shaking. Hi5 cells are infected using the following protocol:

- 15 - Cells at a density of 1×10^6 cells/mL are spun down at 1000 rpm (Beckman GS-6KR centrifuge) for 10 minutes.
- Cells are resuspended in 10% of their original volume in a sterile 50 mL conical centrifuge tube wrapped with aluminum foil. Virus is added at a Multiplicity of Infection (MOI) of 3 and incubated for 1 hour at room temperature with gentle shaking.
- 20 - This cell/virus mix is added to the appropriate volume of medium to attain the original volume and incubated at 27°C with constant shaking for 72 hours.
- Cells are spun down in 50 mL conical centrifuge tubes at 1000 rpm for 10 minutes. Each of the resulting pellets are resuspended in 10 mL of cold (4°C) membrane buffer (25 mM HEPES, pH 7.4, 140 mM NaCl, 1.2 mM MgCl₂, 2.5 mM CaCl₂, 10 25 μ G/mL Aprotinin, 10 μ G/mL Leupeptin) and Dounce homogenized using 10-12 strokes. Dilute to 30 mL with buffer and centrifuge at 18,000 rpm, 4°C, 15 minutes (Sorvall RC5C Centrifuge). The resulting pellet is resuspended in cold membrane buffer in a total of 1/4 of the original volume by vortexing and aspiration using a syringe and 27 gauge

needle.

Protein content is determined (Bradford, Bio-Rad Protein Assay). Membranes are aliquoted in microcentrifuge tubes and quick frozen in liquid nitrogen. Store at -80°C until use.

5 The membrane binding buffer is composed of 25 mM HEPES, pH 7.4, 140 mM NaCl, 1.2 mM MgCl₂, 2.5 mM CaCl₂, 0.1% BSA. 160 µL of membrane binding buffer containing 0.5 µg membrane protein is added to 20 µL of 1.0 nM [¹²⁵I]-NDP-α-MSH (final concentration is 0.1 nM) and 20 µL of competing drug or buffer and incubated for 90 minutes at 37 °C.

10 The mixture is filtered with Brandel Microplate 96 filter apparatus using 96-well GF/B filter presoaked in 1-% polyethyleneimine (Sigma). The filter is washed (4 times with a total of 1 mL per well) with cold wash buffer consisting of 20 mM HEPES, pH 7.4, 5 mM MgCl₂.

15 The filter is dried and punched into a 96 well sample plate (Wallac, 1450-401). 100 µL of Wallac Optiphase Supermix scintillation fluid is added to each well. The top is sealed and the plates are shaken to insure that the filters are thoroughly soaked with fluid. Plates are then counted in a Wallac Microbeta Trilux Scintillation and Luminescence Counter (Model 1450). Dose-response curves are fitted by linear regression analyses and IC₅₀ values are calculated using ExcelFit.

20 B. Functional assay.

Functional membrane based [³⁵S]GTPγS binding assays are developed to discriminate agonists and antagonists.

25 Membrane preparation. Cells (HEK-293 cells expressing the human MC4R) are grown in Minimum Essential Medium with Earle's salts and L-glutamate (Life Technologies, Cat. # 11095-080) containing 10% heat-inactivated fetal bovine serum, 400µg/mL geneticin and 100 mM sodium pyruvate in T175 flasks. Upon reaching confluence, cells are dissociated from tissue culture flasks by rinsing with Ca²⁺ and Mg²⁺ free phosphate buffered saline (Life Technologies, Cat. # 14190-144) and detached

following 5 minutes incubation at 37°C with enzyme free cell dissociation buffer (Life Technologies, Cat. # 13151-014). Cells are collected by centrifugation and resuspended in membrane preparation buffer consisting of 20 mM HEPES, pH 7.4, 10 mM EDTA, 10 µg/mL aprotinin and 10 µg/mL leupeptin. The suspension is homogenized by polytron 5 PT3000 for 30 sec at 20,000 rpm, and centrifuged at 35,000 x g for 15 minutes at 4 °C. The pellet is resuspended in membrane preparation buffer and the last centrifugation is repeated. The final pellet is resuspended in membrane storage buffer consisting of 20 mM HEPES, pH 7.4, 0.1 mM EDTA, 10 µg/mL aprotinin and 10 µg/mL leupeptin. Protein concentration is determined by the Bio-Rad method (Bio-Rad, Cat.# 500-0006) 10 and the preparation is diluted to a final protein concentration of 1 mg/mL. Aliquots are stored at -70°C until used.

[³⁵S]GTPγS membrane binding assay. Compounds are dissolved at 10 mM concentration in DMSO and diluted to the requited concentration into assay buffer. GTPγS to determine nonspecific binding is prepared at 100 µM concentration in assay 15 buffer. The final concentration of DMSO in the assay is 1%. The assay buffer is consisting of 20 mM HEPES, pH 7.4, 100 mM NaCl, 5 mM MgCl₂, 0.5 µM GDP, 10 µg/mL saponin, 10 µg/mL aprotinin and 10 µg/mL leupeptin. The assay is composed by adding 50 µL 10X drug solution, 200 µL membrane preparation (containing 2-4 µg protein), 50 µL [³⁵S]GTPγS (100,000-150,000 CPM) and 200 µL assay buffer to achieve 20 a total volume of 500 µL. The assay mixture is incubated at room temperature for exactly 30 minutes. The reaction is terminated by rapid filtration under vacuum through Whatman GF/B filters using a Brandel 96 wells cell harvester, followed by washing four times with cold wash buffer consisting of 20 mM HEPES, pH 7.4, and 5 mM MgCl₂. The filters are air-dried and 200µL Wallac, Optiphase Super Mix, liquid scintillation cocktail 25 is added to each filter. The bound radioactivity (CPM) is determined by Wallac Trilux 1450 MicroBeta liquid scintillation and Luminescence counter after six hours.

Data interpretation. NDP-α-MSH is used as reference compound and its maximal stimulation is measured at 1 µM (Ref CPM 100%). Total drug-independent binding (Total CPM) is measured in the absence of compounds. Response triggered by

compounds is expressed as percent NDP- α -MSH response. Compound dose response curves are generated by Excel XL Fit. The top of the curve represents the compound's intrinsic activity expressed as % of maximal stimulation.

C. Radioligand binding assays.

5 Binding of [125 I]-(Nle⁴, D-Phe⁷)- α -MSH to human melanocortin receptors was performed using membrane homogenates from Hi5 cells that express recombinant MC4 receptors (Hi5-MC4 cells) and from HEK-293 cells that express recombinant MC3 receptors (HEK-MC3 cells) or MC5 receptors (HEK-MC5 cells) as well as from HBL cells expressing the human MC1R receptor. Homogenates (~0.5 μ g protein/well) were
10 incubated with [125 I]-(Nle⁴,D-Phe⁷)- α -MSH (100 pM for assays with MC4 receptors and 50 pM for assays with MC3/5 receptors) and increasing concentrations of competitors (final concentration of DMSO = 1%) for 90 min at 37°C in buffer consisting of 25 mM HEPES (pH 7.4), 140 mM NaCl, 2.5 mM CaCl₂, 1.2 mM MgCl₂ and 0.1% BSA (10 μ g/ml aprotinin and 10 μ g/ml leupeptin were added to assays with MC3/5 receptors).
15 Assays were stopped by addition of cold wash buffer (20 mM HEPES and 5 mM MgCl₂ for assays with MC4 receptors and 20 mM HEPES for assays with MC3/5 receptors). Filtration over glass fiber filters (Whatman GF/B previously soaked in 1% PEI for assays with MC4 receptors or 0.5% PEI for assays with MC3/5 receptors) was performed using a Brandel cell harvester. Non-specific binding was defined with 1 μ M NDP- α -MSH.

20

Abbreviations

Boc = tert-butoxycarbonyl
CBZ =benzyloxycarbonyl
DCE = 1,2-dichloroethane
25 DCM = dichloromethane
DEA = diethylamine
DMAP = 4-dimethylaminopyridine
DMF = N,N-dimethylformamide
DMSO = dimethylsulfoxide
30 EDC or EDCl = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride
Et = ethyl
EtOH = ethanol
EtOAc = ethyl acetate
Et₃N = triethylamine

EtOAc = ethyl acetate
Et₂O = diethyl ether
FMOC = fluorenlymethoxycarbonyl
HCl = hydrogen chloride
5 HOBT or HOBT = hydroxybenzotriazole hydrate
LiOH = lithium hydroxide
Na₂SO₄ = sodium sulfate
NaOH = sodium hydroxide
NMM = N-methylmorpholine
10 Me = methyl
MeOH = methanol
Ph = phenyl
THF = tetrahydrofuran
TFA = trifluoroacetic acid
15 mp = melting point
tlc = thin layer chromatography
RT = room temperature
h = hours
min. = minute or minutes
20 mmol = millimole
sat'd = saturated
CH₂Cl₂ = methylene chloride
HPLC = high pressure liquid chromatography
LRMS = low resolution mass spectrometry
25

In the examples, when a letter is used in a parenthetical or superscript following the term HPLC, MS, or HPLC/MS, as in "HPLC/MS (A)", "LC/MS (B)", MS Data^a, or following the data, such as 3.28^a, the letter denotes the conditions used for the HLPC/MS,
30 as follows:

- 5 **Method A:** Column Primesphere C18-HC 4.6 x 30 mm, gradient time: 2 min., Hold time: 1 min., Flow rate: 4 mL / min, Detector Wavelength: 220 nM, Solvent A = 10 % AcCN / 90 % H₂O / 5mM NH₄OAc, Solvent B = 90 % AcCN / 10 % H₂O / 5mM NH₄OAc, Start % B = 0 / Finish % B = 100;
- 10 **Method B:** Column Primesphere C18-HC 4.6 x 30 mm, gradient time: 2 min., Hold time: 1 min., Flow rate: 4 mL / min, Detector Wavelength: 220 nM, Solvent A: 10 % AcCN / 90 % H₂O / 0.1 % TFA, Solvent B: 90 % AcCN / 10 % H₂O / 0.1 % TFA, Start % B = 0 / Finish % B = 100;
- 15 **Method C:** Column Primesphere C18-HC 4.6 x 30 mm, gradient time: 3 min., Hold time: 1 min., Flow rate: 4 mL / min, Detector Wavelength: 220 nM, Solvent A: 10 % AcCN / 90 % H₂O / 0.1 % TFA, Solvent B: 90 % AcCN / 10 % H₂O / 0.1 % TFA, Start % B = 0 / Finish % B = 100, Detector Wavelength: 220 nM;
- 20 **Method D:** Column: Premisphere 5μ -C8 21 x 100 mm, acetonitrile-5 mM NH₄OAc/water: 7 min. gradient from 20% AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min.);
- 25 **Method E:** Column: YMC ODS-A C18 4.6 x 150 mm; Flow rate: 1 mL / min, Solvent system: 0-100% B in 30 min. Solvent A: 10% CH₃CN - 90 % H₂O - 5mM NH₄OAc; Solvent B: 90% CH₃CN - 10 % H₂O - 5mM NH₄OAc; UV: 220 nm;
- 30 **Method F:** Column: CombiScreen C8 S-5 4.6 x 50 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH₃CN - 90 % H₂O - 5mM NH₄OAc; Solvent B: 90% CH₃CN - 10 % H₂O - 5mM NH₄OAc; UV: 220 nm;
- 35 **Method G:** Column: CombiScreen C8 S-5 4.6 x 50 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 4 min. Solvent A: 10% CH₃CN - 90 % H₂O - 0.1% TFA; Solvent B: 90% CH₃CN - 10 % H₂O - 0.1% TFA; UV: 220 nm;
- 40 **Method H:** Column: YMC ODS-A C18 4.6 x 150 mm; Flow rate: 1 mL / min, Solvent system: 30-100% B in 30 min. Solvent A: 10% CH₃CN - 90 % H₂O - 0.1% TFA; Solvent B: 90% CH₃CN - 10 % H₂O - 0.1% TFA; UV: 220 nm;
- 45 **Method I:** Assignation from another HPLC analysis (with 0.1 % TFA);
- 50 **Method J:** Column: Premisphere-5u C8 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% (90% CH₃CN - 10 %H₂O - 5mM NH₄OAc), 2 min. gradient; UV: 220 nm;
- 55 **Method K:** Column: YMC S5 C18 4.6 x 150 mm, Flow rate: 1 mL / min, Solvent system: 0-100% (90% CH₃CN - 10 %H₂O - 5mM NH₄OAc), 30 min. gradient; UV: 220 nm;

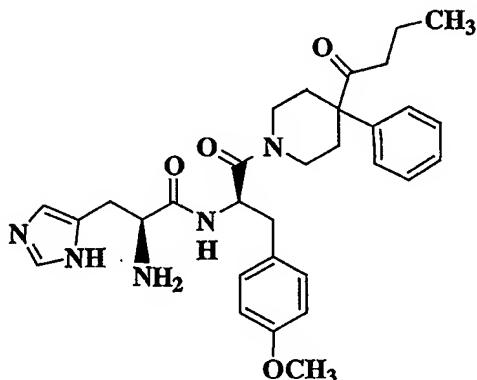
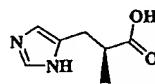
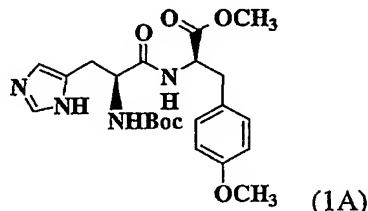
Method L: Column: Xterra- C8 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH₃CN - 90 %H₂O – 5mM NH₄OAc; Solvent B: 90% CH₃CN - 10 %H₂O – 5mM NH₄OAc; UV: 220 nm;

5

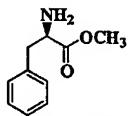
Method M: Column: YMC-Pack S5 Phenyl 4.6 x 50 mm; Flow rate: 3 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH₃CN - 90 % H₂O – 0.05 % TFA; Solvent B: 90% CH₃CN - 10 %H₂O – 0.05 % TFA; UV: 220 nm.

10

EXAMPLE 1

15 **Step A:**

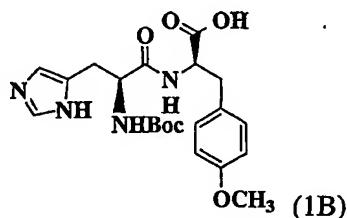
To a solution of N-Boc-L-histidine [] (3.1 g, 12.7 mmol), EDC (3.6 g, 19.1 mmol), HOBT (2.6 g, 19.1 mmol), DMAP (0.16 g, 1.3 mmol) in CH₂Cl₂, and DMF (1:1, 50 mL) were added Et₃N (8.8 mL, 64.0 mmol) and D-4-methoxyphenylalanine



methyl ester hydrochloride [.HCl] (2.9 g, 12.0 mmol), sequentially. The reaction

mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (200 mL), NaOH (0.5 N, 200 mL), and water (200 mL). The organic layer was dried over anhydrous Na₂SO₄, and the solvent was subsequently removed under reduced pressure. The resulting compound 1A was >90% pure as judged by HPLC and used without further purification in Step B.

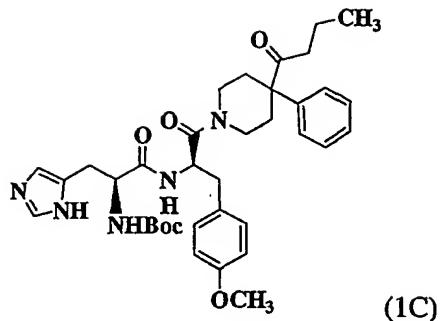
Step B:



To a solution of Compound 1A (12.0 mmol) in CH₃OH (13 mL) was added NaOH (2N, 13 mL) to make the final concentration of NaOH ~1 N. This solution was stirred at RT for 2 h before being diluted with water (100 mL). The aqueous layer was extracted with Et₂O (100 mL X 2), and the organic matter was discarded. The aqueous layer was acidified with HCl (6 N) to pH ~ 2, and extracted with EtOAc (100 mL X 2). The combined organic layers were dried over anhydrous Na₂SO₄, and the solvent was subsequently removed under reduced pressure. The resulting Compound 1B was a white solid with a purity >90% as judged by HPLC. This intermediate was used without further purification for Step C.

20

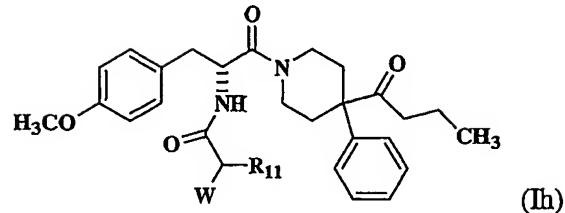
Step C:



- To a solution of Compound 1C (0.5 g, 1.1 mmol), EDC (0.3 g, 1.6 mmol), HOBT (0.22 g, 1.6 mmol), and DMAP (0.13 g, 1.1 mmol) in CH₂Cl₂ (25 mL) were added Et₃N (0.8 mL, 5.5 mmol) and 4-butyryl-4-phenyl-piperidine hydrochloride (0.35 g, 1.3 mmol) sequentially. The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with HCl (0.5 N, 100 mL), water (100 mL), NaOH (0.5 N, 100 mL), and water (100 mL). The organic layer was dried over anhydrous Na₂SO₄, and the solvent was subsequently removed under reduced pressure.
- 5 The resulting Compound 1C was >90% pure as judged by HPLC and used directly without further purification in Step D.
- 10

Step D: Deprotection of Compound 1C

- 15 To a solution of the Boc-protected Compound 1C (1.1 mmol) in wet CH₂Cl₂ (20 mL plus 1 mL water) was added TFA (10 mL). The solution was stirred at RT for 1 h before the solvents were removed. The crude reaction mixture was purified by preparative HPLC to obtain Example 1 at >95% purity as judged by HPLC. HPLC (min) = 2.5, MS (M+H)⁺ = 546.4.

EXAMPLES 2-84

5

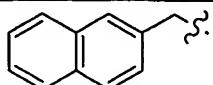
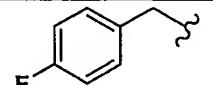
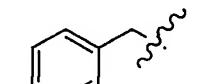
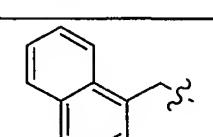
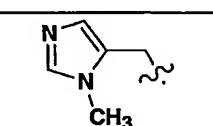
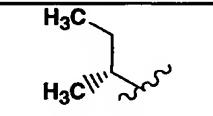
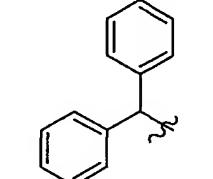
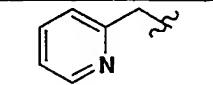
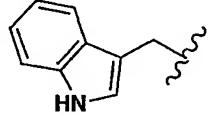
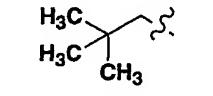
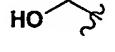
Compounds of formula (Ih), above, wherein the groups R₁₁ and W have the values listed in Table 1, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step A.

10

TABLE 1

Ex No.	R ₁₁	W	Purity (%)	HPLC Ret. time (min)	Mass (M+H)
2			89	3.3	572.49
3	-CH ₃		90	3.2	480.46
4	-CH ₂ -OH		89	3.2	496.49
5	-CH ₂ CH ₃		85	3.2	494.49
6			92	3.0	522.33
7			90	3.2	510.45

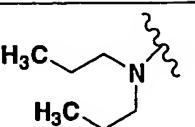
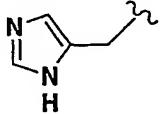
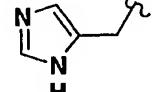
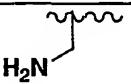
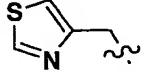
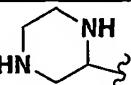
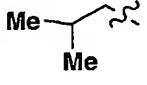
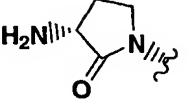
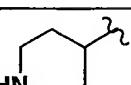
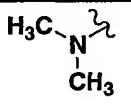
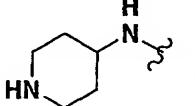
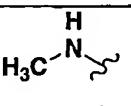
8		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	91	2.5	546.36
9		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	81	3.3	508.46
10		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	76	3.5	522.51
11		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	95	2.7	636.21
12		$\text{H}_2\text{N}-\text{C}(=\text{O})-\text{CH}_3$	92	3.4	522.5
13		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	80	3.3	542.41
14		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	77	3.0	522.24
15		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	82	3.4	542.48
16		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	89	3.0	586.19
17		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	75	3.0	522.17
18		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	90	2.8	636.26
19		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	100	3.5	570.31
20		$\text{H}_2\text{N}-\text{C}(=\text{O})-$	92	2.5	560.39

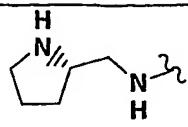
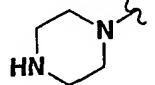
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22			96	3.0	574.22
23			95	2.5	557.3
24			96	3.7	606.32
25			94	2.5	560.15
26			87	2.9	522.26
27			93	3.7	632.32
28			76	2.8	557.13
29			81	3.2	612.2
30			88	3.1	536.29
31	$-CH_3$		96	2.7	480.04
32			93	2.6	496.23

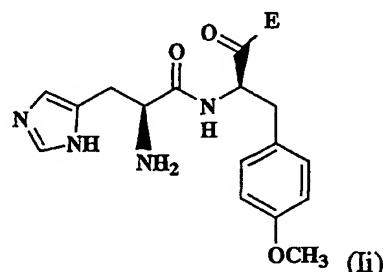
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34	<chem>Cc1ccccc1</chem>	<chem>N[C@@H](C)C</chem>	95	3.0	556.38
35	<chem>-CH3</chem>	<chem>N[C@@H](C)C</chem>	91	2.7	494.22
36	<chem>CC(C)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	89	2.9	522.17
37	<chem>COCCN</chem>	<chem>N[C@@H](C)C</chem>	83	2.7	510.28
38	<chem>CCOCc1ccc(cc1)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	87	3.1	600.19
39	<chem>CCOCc1ccc(cc1)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	92	3.1	600.14
40	<chem>CC(O)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	95	2.7	510.21
41	<chem>O=[N+]([O-])c1ccc(cc1)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	91	2.9	601.33
42	<chem>CC(C)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	89	2.8	522.3
43	<chem>Cc1ccncc1</chem>	<chem>N[C@@H](C)C</chem>	96	2.9	557.48
44	<chem>Clc1ccc(cc1)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	89	3.1	590.09
45	<chem>CC(N)CC[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	96	2.5	523.22
46	<chem>Clc1ccc(cc1)C[C@H](N)C</chem>	<chem>N[C@@H](C)C</chem>	76	3.2	624.07

47			82	2.9	570.14
48			79	3.7	630.33
49			86	3.1	633.88
50			90	3.0	582
51			96	3.1	590.23
52			87	3.2	590.06
53			82	3.1	587.87
54			89	3.0	574.28
55			91	2.9	557.47
56	-CH ₃		97	2.7	494.27
57			90	3.7	662.07
58			83	3.2	682.1

59		$\text{H}_2\text{N}/\text{H}_2\text{S}$	95	3.7	662.24
60		$\text{H}_2\text{N}/\text{H}_2\text{S}$	87	3.3	712.44
61		$\text{H}_2\text{N}/\text{H}_2\text{S}$	79	3.1	660.2
62		$\text{H}_2\text{N}/\text{H}_2\text{S}$	92	3.9	730
63		$\text{H}_2\text{N}/\text{H}_2\text{S}$	92	2.56	571.37
64		$\text{H}_2\text{N}/\text{H}_2\text{S}$	92	2.51	571.32
65		H_2N	91	2.52	585.46
66		$\text{H}_2\text{N} \text{H}_2\text{S}$	82	3.07	605
67		$\text{H}_2\text{N}/\text{H}_2\text{S}$	92	2.5	537.44
68		$\text{H}_2\text{N}/\text{H}_2\text{S}$	90	4.3	595
69		$\text{H}_2\text{N}/\text{H}_2\text{S}$	91	2.48	509.33
70		$\text{H}_2\text{N}/\text{H}_2\text{S}$	94	2.51	571.35

71			94	2.9	564.44
72			93	2.71	547.28
73			93	2.71	636.35
74			93	2.47	495.29
75			88	2.79	563.23
76	H		90	3.1	466.46
77	H		89	2.54	535.33
78			82	3.07	605
79	H		91	2.76	534.33
80	H		93	2.71	494.31
81	H		90	2.52	549.32
82	H		80	2.66	480.27

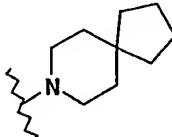
83	H		89	2.52	549.31
84	H		92	2.66	535.34

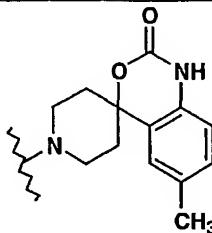
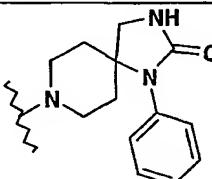
EXAMPLES 85-88

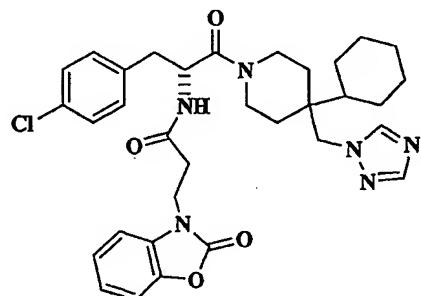
Compounds of formula (II), above, wherein the group E has the values shown in Table 2, were prepared following the same procedures as described above for Example 1.

10

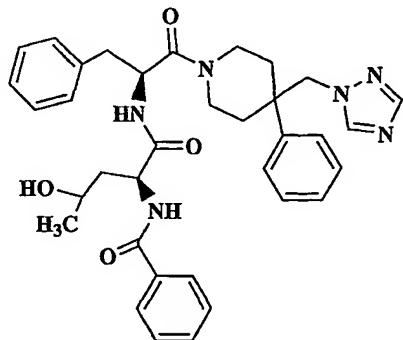
TABLE 2

Ex. No.	E	Purity (%)	HPLC RT (min)	Mass (M+H)
85		95	2.43	454
86		98	1.96	532

87		95	2.11	547
88		90	2.03	546

EXAMPLE 89

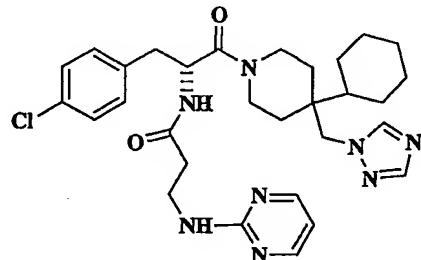
Example 89 was prepared following the same or similar procedure described
 10 herein for Example 1. Purity 86.0%, HPLC ret. time = 3.1, MS $(M+H)^+=619.38$.

EXAMPLE 90

Example 90 was prepared following the same or similar procedure described
5 herein for Example 1. Purity 93%, HPLC ret. time = 3.8 min, MS $(M+H)^+$ = 635.42.

EXAMPLE 91

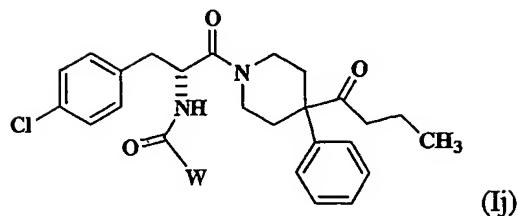
10 N-[1-(4-Chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-3-(pyrimidin-2-ylamino)-propionamide



15 To a solution of Example 171 (35 mg, 0.07 mmol) and 2-bromopyrimidine (14 mg, 0.09 mmol) in EtOH (1.0 mL) at RT was added potassium carbonate (14 mg, 0.1 mmol). The mixture was heated to 60°C and stirred overnight at 60°C. The mixture was cooled to RT a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x 25 mL), and the combined organic layers were dried ($MgSO_4$ anh.), filtered, and evaporated to afford an oil (>80% purity by LCMS). The residue was purified using preparative HPLC and after evaporation, the residue was lyophilized to afford 32 mg (80% yield) of Example 91. This semi-solid was converted as its hydrochloride salt. HPLC/MS (A), ret. time = 1.68 min, purity 98.4%, MS pos. m/z 579 ($M+H)^+$; HPLC / MS (E), ret. time = 24.13 min, purity 97.4% 1H NMR (400 MHz, MeOH-d₄) δ ppm (two rotamers; 1:1.5 ratio) 8.45 (1H, s, minor rotamer), 8.44 (1H, s, major rotamer), 8.28 (2H, t, J = 4.6 Hz), 7.99 (1H, s, minor rotamer), 7.95 (1H, s, major rotamer), 7.31 (2H, d, J = 8.3 Hz, major rotamer), 7.27 (2H, d, J = 8.4 Hz, minor rotamer), 7.24 (2H, d, J = 8.6 Hz, major rotamer), 7.20 (2H, d, J = 8.4 Hz, minor rotamer), 6.63 (1H, t, J = 4.8 Hz), 5.09 (1H, m), 4.30 (2H, s, major rotamer), 4.26 (2H, s, minor rotamer), 3.64-3.45 (6H, m), 2.95 (2H, m), 2.52 (2H, m), 1.81-0.88 (15H, m).

EXAMPLES 92-113

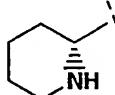
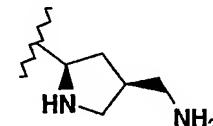
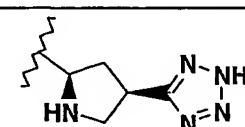
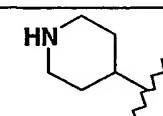
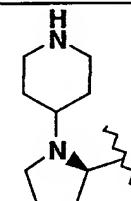
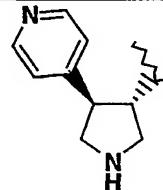
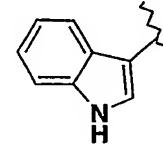
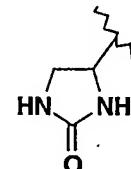
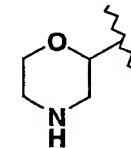
5



Compounds of formula (Ij), above, wherein the group W has the values listed in Table 3, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step A.

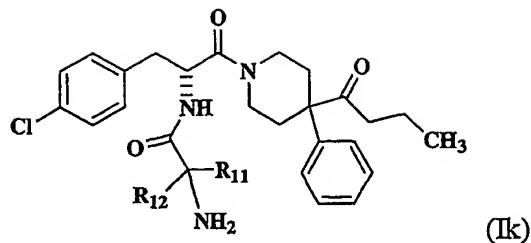
TABLE 3

Ex. No.	W	Purity (%)	HPLC RT (min)	Mass (M+H)
92		87	3.2	506.5
93		91	3.2	522.45
94		81	3.1	524.23
95		82	2.8	520.25
96		94	3.0	612.28

97		96	2.7	520.43
98		92	2.5	535
99		85	2.72	574
100		93	2.73	520.41
101		93	2.56	589.52
102		96	2.54	583.38
103		96	2.95	554.28
104		85	4.31	521
105		79	2.73	522.3

106		91	2.52	521.33
107		92	2.5	521.33
108		80	2.82	531.28
109		94	2.72	520.36
110		86	2.8	548.34
111		86	2.8	563.27
112		80	2.74	520.33
113		92	2.49	549.33

EXAMPLES 114-115

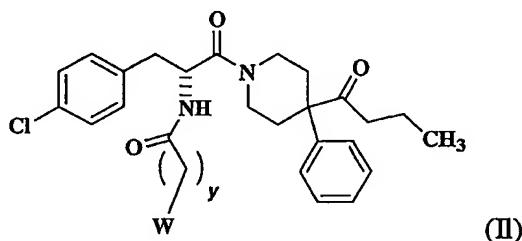


Compounds of formula (Ik), above, wherein the groups R₁₁ and R₁₂ have the values listed in Table 4, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step A.

TABLE 4

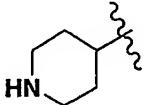
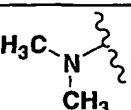
Ex. No.	R ₁₁	R ₁₂	Purity (%)	HPLC RT (min)	Mass (M+H)
114	-CH ₃	-CH ₃	92	3.2	494.49
115	△		95	2.7	492.25

10

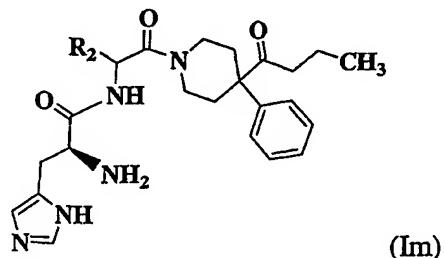
EXAMPLES 116-117

15 Compounds of formula (II), above, wherein the integer y and group W have the values listed in Table 5, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step A.

TABLE 5

Ex. No.	y	W	Purity (%)	HPLC RT (min)	Mass (M+H)
116	2		96	2.79	548.34
117	4		95	2.74	536.36

5

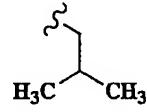
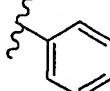
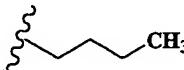
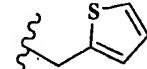
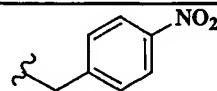
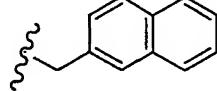
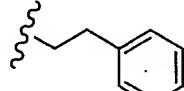
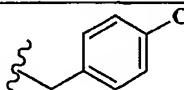
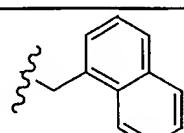
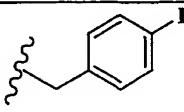
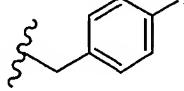
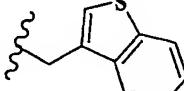
EXAMPLES 118-157

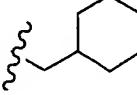
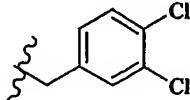
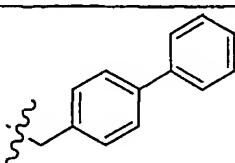
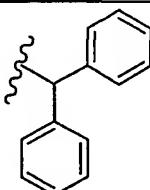
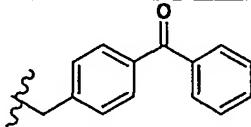
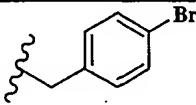
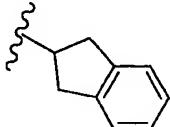
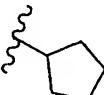
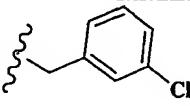
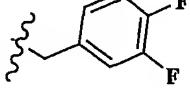
10 Compounds of formula (Im), above, wherein R₂ has the values listed in Table 6, were prepared following the same procedure described for Example 1, except a different methyl ester hydrochloride was used in place of methoxyphenylalanine methyl ester hydrochloride in Step A.

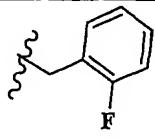
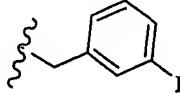
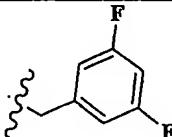
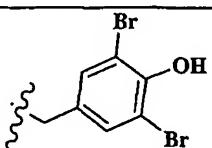
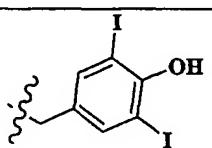
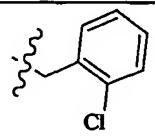
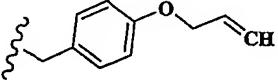
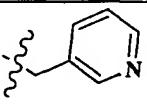
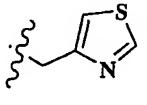
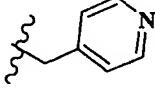
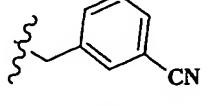
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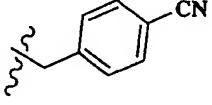
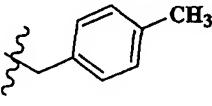
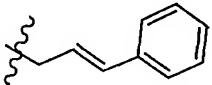
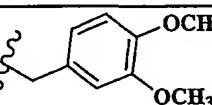
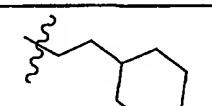
TABLE 6

Ex. No.	R ₂	Purity (%)	HPLC RT (min)	Mass (M+H)

118		76	3.0	482.36
119		74	2.9	502.35
120		75	3.0	482.36
121		87	3.0	522.32
122		86	3.0	561.3
123		93	3.3	566.33
124		78	3.2	530.37
125		89	3.2	550.29
126		85	3.3	566.34
127		84	3.1	534.35
128		78	3.3	642.24
129		88	3.3	572.32

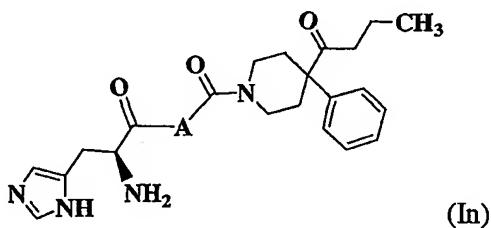
130		87	3.3	522.43
131		90	3.4	584.26
132		89	3.5	592.38
133		90	3.3	592.38
134		84	3.2	620.38
135		92	3.3	594.25
136		88	3.2	542.36
137		93	3.0	494.36
138		92	3.2	550.29
139		84	3.1	552.31

140		79	3.0	534.34
141		78	3.1	534.36
142		76	3.1	552.33
143		89	3.0	690.16
144		93	3.1	784.11
145		93	3.1	550.32
146		84	3.2	572.38
147		88	2.3	517.4
148		79	2.7	523.35
149		90	2.3	517.4
150		84	2.8	541.38
151	H	84	2.5	426.35

152	-CH ₃	85	2.5	440.35
153		85	2.8	541.36
154		73	3.2	530.41
155		83	3.2	542.4
156		89	2.8	576.4
157		77	3.5	536.46

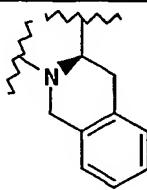
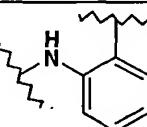
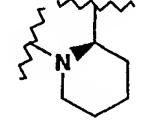
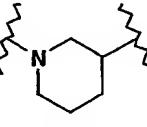
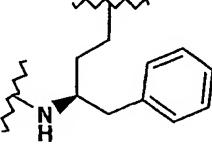
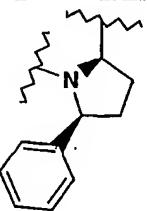
EXAMPLES 158-167

5

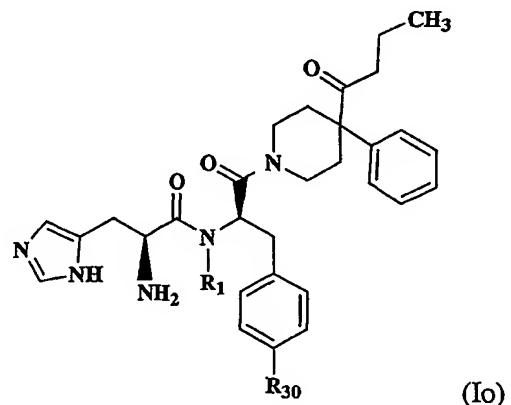


Compounds of formula (In), above, wherein A has the values listed in Table 7 {wherein in compounds of formula (I), A = X(R₁)-CH(R₂)-CH(R₃)_r-(CH₂)_s-}, were prepared following the same procedure described for Example 1, except a different 10 methyl ester hydrochloride was used in place of methoxyphenylalanine methyl ester hydrochloride in Step A.

TABLE 7

Ex. No.	A	Purity (%)	HPLC RT (min)	Mass (M+H)
158	-CH ₂ CH ₂ -	82	2.6	440.32
159		73	2.9	528.37
160		88	2.8	488.33
161		71	2.8	480.34
162		84	2.7	480.36
163		89	3.1	544.39
164		85	3.0	542.38
165		74	3.1	542.39

166		90	3.1	542.4
167		83	3.0	528.39

EXAMPLES 168-170

Compounds of formula (Io), above, wherein the groups R_1 and R_{30} have the values listed in Table 8, were prepared following the same procedure as for Example 1, except a different methyl ester hydrochloride was used in Step A.

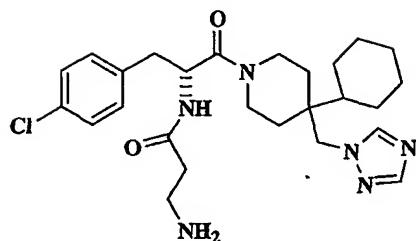
10

TABLE 8

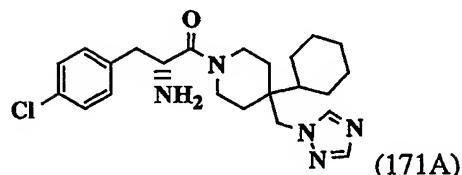
Ex. No.	R_1	R_{30}	Purity (%)	HPLC RT (min)	Mass ($M+H$)
168	H	Cl	90	3.08	551
169	H	H	86	2.88	515
170	CH ₃	Cl	85	3.26	565

EXAMPLE 171

5

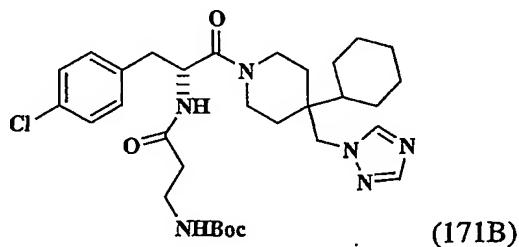
Step A:

10



Compound 171A was prepared by coupling of commercially available N-BOC D-

4-chlorophenylalanine and 4-Cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidine , followed by deprotection of the BOC group, as described in WO 00/74679, incorporated herein by reference.

Step B:

To a solution of α -amino amide from step A (1.1 g, 2.56 mmol) and N-Boc- β -alanine (531 mg, 2.81 mmol) in DCM (12 mL) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (736 mg, 3.8 mmol) and HOBT (518 mg, 3.8 mmol) at RT. The mixture was stirred at RT overnight and a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x

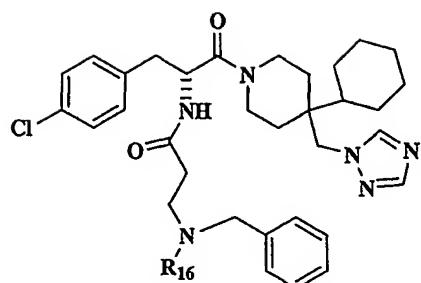
25 mL), and the combined organic layers were dried (MgSO_4 anh.), filtered, and evaporated to afford compound 171A which was used in the next step without purification.

Step C: Example 171

5 To a solution of Compound 171B (1.0 g, 1.7 mmol) in DCM (10 mL) was added a 20% (v/v) solution of TFA in DCM (1.6 mL) at RT. The mixture was stirred at RT for 8 h and evaporated under reduced pressure. The residue was purified using preparative HPLC and after evaporation, the residue was lyophilized to afford 0.9 g (47% yield) of Example 171 as the TFA salt. HPLC/MS (A), ret. time = 1.50 min, purity 86.9%, MS pos. m/z 501 ($\text{M}+\text{H})^+$; HPLC/MS (E), ret. time = 10.81 min, purity 100%; ir (ν_{max} , KBr) cm^{-1} 3600-2880, 1695, 1620; ^1H NMR (400 MHz, MeOH-d₄) δ ppm (two rotamers; 1:2 ratio) 8.43 (1H, s, minor rotamer), 8.42 (1H, s, major rotamer), 7.96 (1H, s, minor rotamer), 7.92 (1H, s, major rotamer), 7.26 (2H, d, J = 8.3 Hz, major rotamer), 7.23 (2H, d, J = 8.4 Hz, minor rotamer), 7.18 (2H, d, J = 8.3 Hz, major rotamer), 7.15 (2H, d, J = 8.6 Hz, minor rotamer), 4.98 (1H, t, J = 7.8 Hz), 4.21 (2H, s, major rotamer), 4.18 (2H, s, minor rotamer), 3.60 (1H, m), 3.31 (3H, m), 3.08 (2H, m), 2.87 (2H, m), 2.54 (2H, t, J = 6.5 Hz), 1.95-0.82 (15H, m). *Anal.* Calc'd for $\text{C}_{26}\text{H}_{37}\text{ClN}_6\text{O}_2\bullet 3\text{CF}_3\text{COOH}\bullet 2\text{H}_2\text{O}$: C, 43.72; H, 5.04; N, 9.56. Found: C, 43.90; H, 4.31; N, 9.16. *Anal.* Calc'd for $\text{C}_{26}\text{H}_{37}\text{ClN}_6\text{O}_2\bullet 3\text{HCl}\bullet \text{H}_2\text{O}$: C, 49.69; H, 6.74; N, 13.37. Found: C, 49.96; H, 6.75; N, 12.88.

EXAMPLES 172 AND 173

25 3-Benzylamino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-propionamide (Ex. 172), and 3-diBenzylamino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-propionamide (Ex. 173)



Example 172: R₁₆ = H

Example 173: R₁₆ = Bz

At RT, benzaldehyde (13 μ L, 0.13 mmol) was added to a solution of Example 171 (48.5 mg, 0.1 mmol) in DCE (1 mL). Sodium triacetoxyborohydride (29 mg, 0.14 mmol) was added, the mixture was stirred at RT for 24 hours, and a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x 25 mL) and the combined organic layers were dried ($MgSO_4$ anh.), filtered, and evaporated to afford 36 mg of an oil which consisted in a (11:1) mixture of Examples 172 and 173, as determined by HPLC/MS. The purification was performed using preparative HPLC (Column: Premisphere 5 μ -C8 21 x 100 mm) HPLC (acetonitrile-5 mM NH₄OAc/water: 7 min. gradient from 50% AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min.), and after evaporation, the residue was lyophilized to afford 24 mg (42% yield) of Ex. 172 along with 6 mg (9% yield) of Ex. 173.

Ex. 172: HPLC / MS (Column: Premisphere- C18 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH₃CN - 90 %H₂O – 5mM NH₄OAc; Solvent B: 90% CH₃CN - 10 %H₂O – 5mM NH₄OAc; UV: 220 nm; Micromass ZMD 2000, ESI): retention time 1.76 min, purity 100%, MS pos. *m/z* 591 (M+H)⁺; HPLC / MS (Column: YMC ODS-A C18 4.6 x 150 mm; Flow rate: 1 mL / min, Solvent system: 30-100% B in 30 min., UV: 220 nm;): retention time 12.13 min, purity 100% ¹H nmr (400 MHz, MeOH-d₄) δ ppm (two rotamers; 1:1.5 ratio) 8.47 (1H, s, minor rotamer), 8.45 (1H, s, major rotamer), 8.02 (1H, s, minor rotamer), 7.97 (1H, s, major rotamer), 7.41 (5H, m), 7.34 (2H, d, J = 8.4 Hz, major rotamer), 7.30 (2H, d, J = 8.3 Hz, minor rotamer), 7.27 (2H, d, J = 8.3 Hz, major rotamer), 7.23 (2H, d, J = 8.6 Hz,

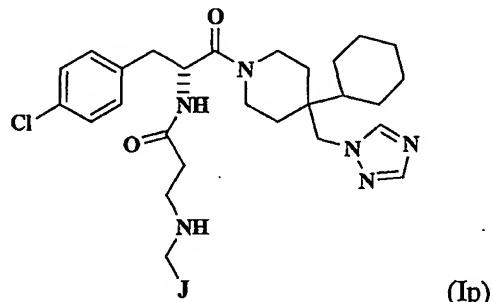
minor rotamer), 5.09 (1H, br. t, $J = 6.8$ Hz), 4.31 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 4.00 (2H, s, major rotamer), 3.96 (2H, s, minor rotamer), 3.75-3.36 (4H, m), 3.00 (4H, m), 2.57 (2H, t, $J = 6.8$ Hz), 1.80-0.89 (15H, m).

- 5 **Ex. 173:** HPLC / MS (Column: Premisphere- C18 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH₃CN - 90 %H₂O - 5mM NH₄OAc; Solvent B: 90% CH₃CN - 10 %H₂O - 5mM NH₄OAc; UV: 220 nm; Micromass ZMD 2000, ESI): retention time 2.45 min, purity 96.7%, MS pos. *m/z* 681 (M+H)⁺; ¹H nmr (400 MHz, MeOH-d₄) δ ppm (two rotamers present; 1:1.4 ratio) 8.46 (1H, s, minor rotamer), 8.42 (1H, s, major rotamer), 8.01 (1H, s, minor rotamer), 7.93 (1H, s, major rotamer), 7.43-7.10 (14H, m), 5.10 (1H, m), 4.30 (2H, s, major rotamer), 4.28 (2H, s, minor rotamer), 3.77 (1H, m), 3.70 (2H, s, minor rotamer), 3.66 (2H, s, major rotamer), 3.66-3.36 (7H, m), 3.01-2.35 (5H, m), 1.90-0.79 (15H, m).
- 10

15

EXAMPLES 174-186

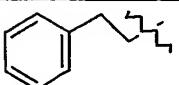
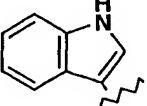
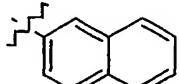
20



Compounds of formula (Ip), above, wherein the group J has the values listed in Table 9, were prepared following the same procedure described for Examples 175-76, using with different aldehydes in place of benzaldehyde.

TABLE 9

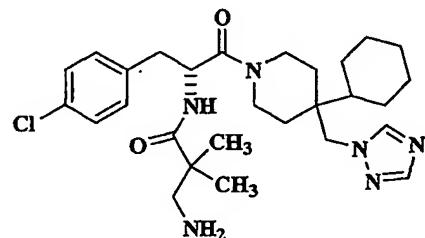
Ex. No.	J	HPLC Retention Time (min) ^b	MS Data ^b (M + H) ⁺
174		1.84	650
175		2.08	668
176		1.80	580
177		2.07	668
178		2.05	668
179		1.75	668
180		1.96	660
181		1.91	659
182		1.97	730
183		1.84	626

184		2.00	618
185		1.92	629
186		2.11	640

EXAMPLE 187

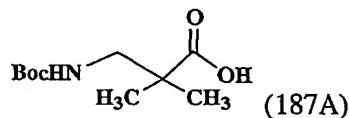
5

3-Amino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-2,2-dimethyl-propionamide



10

Step A:



15

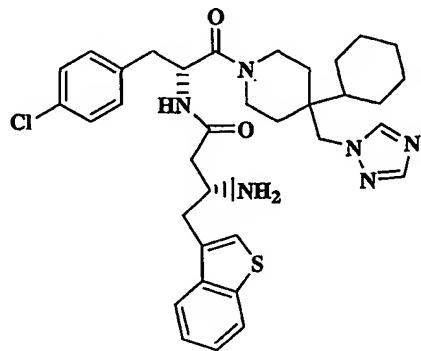
Compound 187A was prepared following the procedure described in Dhokte et al., *Tetrahedron Lett.*, Vol. 39 (1998), at pp. 8771-8774.

Step B:

Example 187 was prepared following the procedure described for the preparation 20 of Example 171, using Compound (187A) in place of Boc-β-alanine in Step A.

- HPLC/MS (F), ret. time 1.64 min, purity 95.7%, MS pos. m/z 529 ($M+H$) $^+$; HPLC / MS (H), ret. time = 12.12 min, purity 95.1%; 1 H NMR (400 MHz, MeOH-d₄) δ ppm (two rotamers; 1:1.4 ratio) 8.56 (1H, s, minor rotamer), 8.53 (1H, s, major rotamer), 8.08 (1H, s, minor rotamer), 8.02 (1H, s, major rotamer), 7.36 (2H, d, J = 8.4 Hz, major rotamer),
 5 7.34 (2H, d, J = 8.9 Hz, minor rotamer), 7.28 (2H, d, J = 8.3 Hz, major rotamer), 7.25 (2H, d, J = 8.4 Hz, minor rotamer), 5.07 (1H, m), 4.32 (2H, s), 3.68-3.34 (4H, m), 3.02 (4H, m), 1.98-0.99 (15H, m), 1.34, 1.24 (6H, 2s, minor rotamer), 1.33, 1.28 (6H, 2s, major rotamer).

10

EXAMPLE 188

15

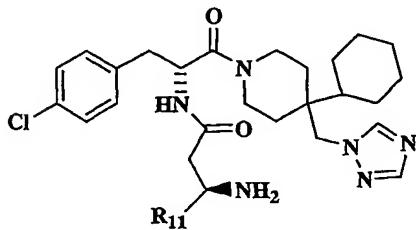
Example 188 was prepared using the same procedure as described for the

preparation of Example 171, starting with β -amino acid HOOC- HPLC / MS (E), ret. time = 2.04 min, purity 98.7%, MS pos. m/z 647 ($M+H$) $^+$; HPLC (G), ret. time = 2.75 min, purity 94.8%; MS (Finigan TSQ 7000, ESI) m/z 647 ($M+H$) $^+$; HRMS calculated for C₃₅H₄₃ClN₆O₂S: 647.2925, found: 647.2935 1 H NMR (400 MHz, MeOH-d₄) δ ppm (two rotamers; ratio 1.6:1) 8.71 (1H, s, minor rotamer), 8.64 (1H, s, major rotamer), 8.16 (1H, s, minor rotamer), 8.07 (1H, s, major rotamer), 7.93 (1H, d, J = 8 Hz), 7.82 (1H, t, J = 8 Hz), 7.48-7.38 (3H, m), 7.26 (2H, d, J = 8 Hz), 7.19 (2H, d, J = 8 Hz), 7.18 (1H, d, J = 8 Hz), 5.03-4.95 (1H, m), 4.29 (2H, s), 4.18 (1H, m), 4.12 (1H, m), 3.92-

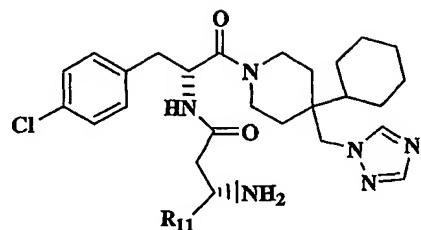
3.75 (1H, m), 3.69-3.59 (4H, m), 3.51-3.35 (1H, m), 3.20-3.06 (2H, m), 2.98-2.80 (2H, m), 2.63-2.48 (2H, m), 1.85-0.85 (14H, m).

EXAMPLES 189-217

5



Core A
(Iq)



Core B

10 Compounds having the formula (Iq), and Core A and B as noted in Table 10, wherein R₁₁ has the values listed in Table 10, were prepared using the same procedure described above for the preparation of Example 171 starting with the appropriately substituted β -

15 amino acid

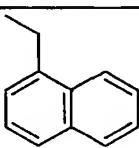
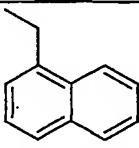
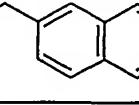
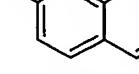
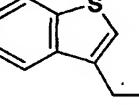
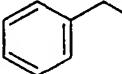
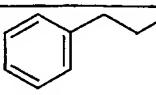
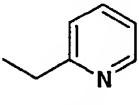
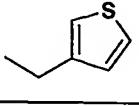
The compounds were prepared via high-throughput synthesis. The crude product was purified either by automated SPE-SCX using a Zymark BenchMate Workstation or Shimadzu automated preparative HPLC system and concentrated *in vacuo*. The SPE workstation was carried out as follows:

- 20 1) Conditioned a SPE column (SCX cation exchange, 1.5 g of sorbent, 0.79 mequiv / g) with 10 mL of methanol (0.25 mL / sec) and 10 mL of a 1:1 mixture methanol / H₂O;
- 2) Loaded reaction contents onto the column (0.05 mL / sec);
- 3) Washed column with 2 x 10 mL of methanol (0.20 mL / sec);
- 4) Eluted column with 2 x 8 mL of 2M ammonia in methanol and collected the effluent into a tared receiving tube (0.10 mL / sec); and
- 5) Concentrated the products using a Savant Speedvac Plus SC210A.

25 Compounds purified by preparative HPLC were diluted in MeOH (2 mL) and purified using a Shimadzu LC-10A automated preparative HPLC system and the following conditions: initial gradient (80 % A, 20 % B) ramp to final gradient (0 % A, 100 % B) over 8 min., hold for 4 min. (0 % A, 100 % B), Solvent A: 10 % AcCN / 90 % H₂O /

5mM NH₄OAc, Solvent B: 90 % AcCN / 10 % H₂O / 5mM NH₄OAc, Column
 Primesphere C18-HC 21.2 x 100 mm, Detector Wavelength: 220 nM.

TABLE 10

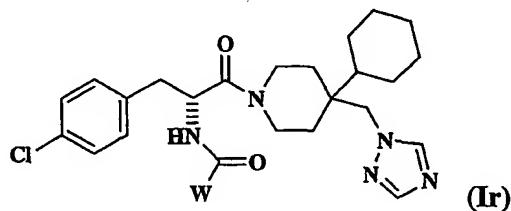
Ex.	Core	R ₁₁	HPLC Retention Time (min)	MS Data (M + H) ⁺
189	B		3.28 ^c	641
190	A		3.21 ^c	641
191	B		3.28 ^c	641
192	A		3.22 ^c	641
193	B		3.28 ^c	647
194	B		1.70 ^b	605
195	A		1.67 ^b	605
196	B		1.37 ^b	592
197	A		1.57 ^b	577
198	A		1.60 ^b	597

199	B		1.38 ^b	592
200	B		1.59 ^b	577
201	B		1.60 ^b	597
202	B		1.62 ^b	597
203	B		1.97 ^b	667
204	A		1.77 ^b	667
205	B		1.14 ^b	581
206	A		0.44 ^b	592
207	A		0.39 ^b	592
208	B		0.30 ^b	592
209	A		1.27 ^b	581
210	A		1.51 ^b	597
211	A		0.94 ^b	592
212	A		1.56 ^b	591

213	A	$(CH_3)_2CHCH_2-$	1.79 ^a	557
214	A	$(CH_3)_2CH-$	1.71 ^a	543
215	A	(S)-(C ₂ H ₅)(CH ₃)C [*] H-	1.76 ^a	557
216	A		1.84 ^a	630
217	A	CH ₃ -	1.62 ^a	515

EXAMPLES 218-237

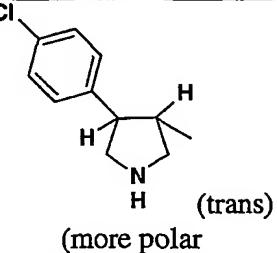
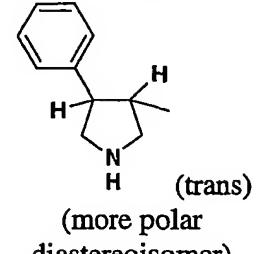
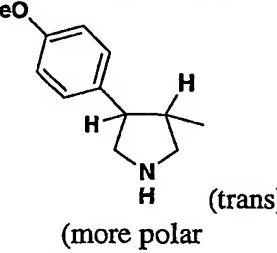
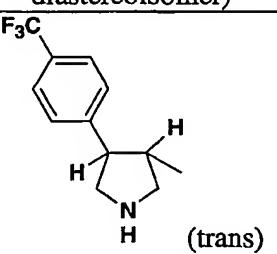
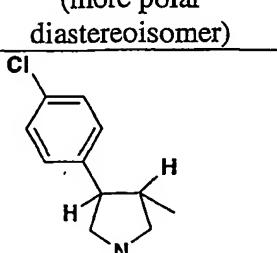
5

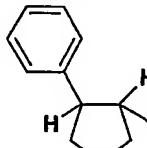
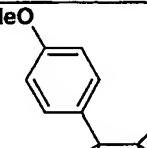
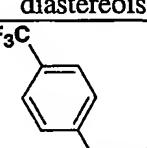
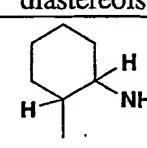
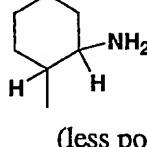
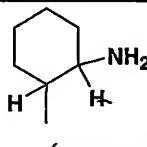


Compounds having the formula (Ir), wherein W has the values listed in Table 11, were prepared using the same or similar procedure described above for the preparation of Examples 187-217.

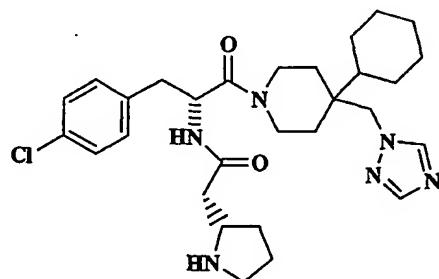
TABLE 11

Ex.	W	HPLC Ret. Time (min)	MS Data (M + H) ⁺
218		1.72 ^a	543
219		1.72 ^a	541
220		1.65 ^a	541
221		1.91 ^a	555

	(less polar diastereoisomer)		
222		1.65 ^a	513
223		1.94 ^a	637
224		1.82 ^a	603
225		1.82 ^a	633
226		1.99 ^a	671
227		2.07 ^a	637

	(less polar diastereoisomer)		
228	 (trans) (less polar diastereoisomer)	1.94 ^a	603
229	 (trans) (less polar diastereoisomer)	1.91 ^a	633
230	 (trans) (less polar diastereoisomer)	2.09 ^a	671
231	 (cis) (more polar diastereoisomer)	1.74 ^a	555
232	 (trans) (less polar diastereoisomer)	1.67 ^a	555
233	 (trans) (more polar diastereoisomer)	1.80 ^a	555

234	CH ₃ NHCH ₂ -	1.83 ^a	501
235		1.89 ^a	513
236		1.82 ^a	513
237	(CH ₃) ₂ NCH ₂ -	1.84 ^a	515

EXAMPLE 238

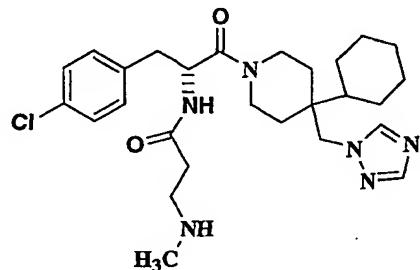
5

Example 238 was prepared following the same procedure described above for Examples 217-237. HPLC (A), ret. time = 1.77, (M+S)⁺=541.

10

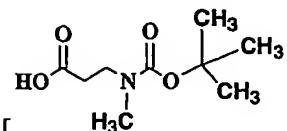
EXAMPLE 239

N-[1-(4-Chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-3-methylamino-propionamide



15

To a solution of Compound 171A (80 mg, 0.19 mmol) and carbamate

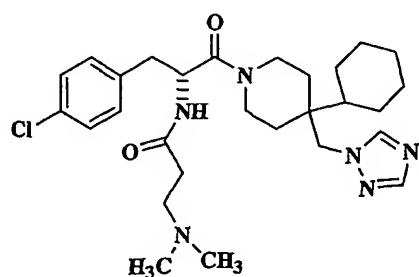


[] (45 mg, 0.22 mmol) in DCM was added EDCI (57 mg, 0.3 mmol) and HOBr (40 mg, 0.3 mmol). The mixture was stirred at RT overnight and a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x 25 mL), and the combined organic layers were dried (MgSO_4 anh.), filtered and evaporated to afford a *tert*-butylcarbamate intermediate. The *tert*-butylcarbamate intermediate was dissolved in DCM (10 mL), and a 20% (v/v) solution of TFA in DCM (1.6 mL) was added at RT. The mixture was stirred at RT for 8 hours and evaporated under reduced pressure. The residue was purified using HPLC and after evaporation, the residue was lyophilized to afford Example 239 as the TFA salt. HPLC / MS (J), ret. time = 1.66 min, purity 100% .Micromass ZMD 2000, ESI): MS pos. *m/z* 515 ($\text{M}+\text{H}$)⁺; HPLC (H), ret. time = 18.78, 1915 min, purity 93.1%). ¹H NMR (400 MHz, MeOH-d₄) δ ppm (two rotamers; 1:1.7 ratio) 8.55 (1H, s, minor rotamer), 8.54 (1H, s, major rotamer), 8.08 (1H, s, minor rotamer), 8.03 (1H, s, major rotamer), 7.35 (2H, d, *J* = 8.3 Hz, major rotamer), 7.29 (2H, d, *J* = 8.4 Hz, minor rotamer), 7.28 (2H, d, *J* = 8.3 Hz, major rotamer), 7.26 (2H, d, *J* = 8.6 Hz, minor rotamer), 5.08 (1H, t, *J* = 7.8 Hz), 4.32 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 3.60 (1H, m), 3.31 (3H, m), 3.08 (2H, m), 2.87 (2H, m), 2.54 (5H, m), 1.95-0.82 (15H, m).

20

EXAMPLE 240

N-[1-(4-Chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-3-dimethylamino-propionamide



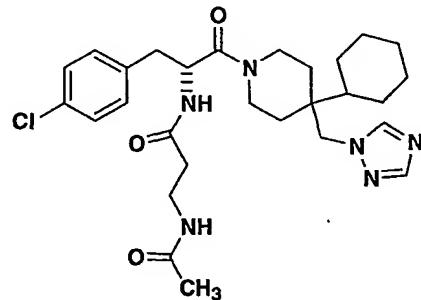
25

To a vigorously stirred solution of Example 171 (45 mg, 0.09 mmol) and formaldehyde (37% w/w in water, 45 μ L, 0.5 mmol) in DCE (1.0 mL) was added sodium triacetoxyborohydride (110 mg, 0.5 mmol) at RT. The mixture was stirred overnight at RT and a sat'd solution of ammonium acetate (5 mL) was added. The separated aqueous layer was extracted with methylene chloride (3 x 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified using preparative HPLC and after evaporation, the residue was lyophilized to afford Example 240 as the TFA salt. HPLC / MS (A), ret. time = 1.74 min, purity 98.2% Micromass ZMD 2000, ESI): MS pos. m/z 529 ($\text{M}+\text{H}$)⁺; HPLC (K), ret. time = 10 19.58 min, purity 84.3%. ¹H NMR (400 MHz, MeOH-d₄), δ ppm (two rotamers; 1:1.7 ratio) 8.56 (1H, s, minor rotamer), 8.53 (1H, s, major rotamer), 8.08 (1H, s, minor rotamer), 8.03 (1H, s, major rotamer), 7.35 (2H, d, J = 8.3 Hz, major rotamer), 7.29 (2H, d, J = 8.4 Hz, minor rotamer), 7.28 (2H, d, J = 8.3 Hz, major rotamer), 7.26 (2H, d, J = 8.6 Hz, minor rotamer), 5.00 (1H, m), 4.31 (2H, m), 3.70-2.85 (11H, m), 2.92 (6H, br. s), 15 2.74 (2H, m), 1.91-0.75 (15H, m).

EXAMPLE 241

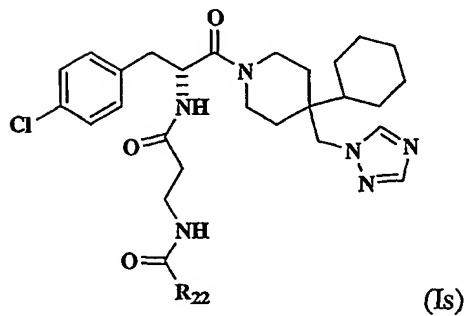
3-Acetylamino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-propionamide

20



Acetyl chloride (25 μ L, 3.3 mmol) was added to a solution of Example 171 (150 25 mg, 3.0 mmol) and Et₃N (50 μ L, 3.6 mmol) in DCM (7 mL) at 0°C. The mixture was stirred at RT overnight and quenched with sat'd ammonium chloride (10 mL). The

separated aqueous layer was extracted with methylene chloride (3 x 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified using preparative HPLC, and after evaporation, the residue was lyophilized to afford Example 241 as the TFA salt. HPLC / MS (A?), ret. time = 1.60 min, purity 91.6%. Micromass ZMD 2000, ESI): MS pos. m/z 543 ($\text{M}+\text{H}$)⁺ ; HPLC (K), ret. time = 20.98 min, purity 92.6%. ¹H NMR (400 MHz, MeOH-d₄) δ ppm (two rotamers; 1:1.6 ratio) 8.56 (1H, s), 8.13 (1H, s), 7.35 (2H, d, J = 8.1 Hz, major rotamer), 7.30 (2H, d, J = 8.1 Hz, minor rotamer), 7.28 (2H, d, J = 8.1 Hz, major rotamer), 7.24 (2H, d, J = 8.6 Hz, minor rotamer), 5.08 (1H, br. t, J = 3.3 Hz), 4.34 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 3.70-2.85 (11H, m), 2.74 (2H, m), 1.96 (3H, s, major rotamer), 1.94 (3H, s, minor rotamer), 1.91-0.75 (15H, m).

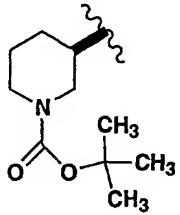
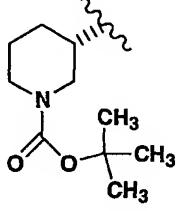
EXAMPLES 242-251

5 Compounds having the formula (Is), wherein R₂₂ has the values listed in Table 12, were prepared using EDCI-HOBt coupling method described above for compound 171B, using an appropriate amino acid in place of Boc-β-alanine.

10

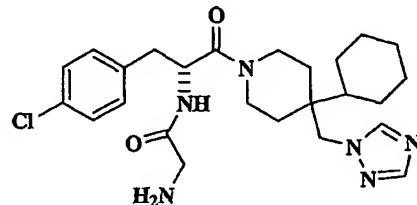
TABLE 12

Ex.	R ₂₂	HPLC Retention Time (min)	MS Data (M + H) ⁺
242		1.57 ^a	594
243		1.64 ^a	604
244	CF ₃ -	1.66 ^a	596
245	CH ₃ CH ₂ -	1.50 ^a	556
246		1.50	639
247	(Me) ₂ NCH ₂ CH ₂ -	1.42	599
248	CH ₃ OCH ₂ -	1.48	572
249		1.64	607

250		1.71	711
251		1.72	711

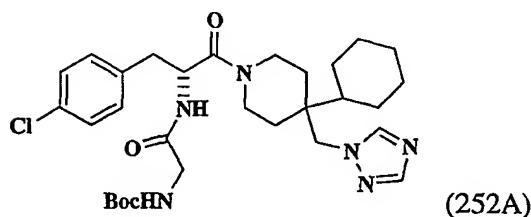
EXAMPLE 252

5 2-Amino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-acetamide



10

Step A:



15

To a solution of compound 171A (83 mg, 0.19 mmol) and N-Boc-glycine (86 mg, 0.49 mmol) in DMF (2 mL) was added EDCI (93 mg, 0.49 mmol), HOBr (66 mg, 0.49 mmol) and DIPEA (135 µL, 0.78 mmol) at RT. The mixture was stirred at RT overnight and water (25 mL) was added. The aqueous layer was extracted with EtOAc (3 x 25 mL)

and the combined organic layers were washed with a solution of sodium bicarbonate (25 mL), water (25 mL), brine (25 mL) dried (Na_2SO_4 anh.), filtered, and evaporated to afford the compound 252A which was used in the next step without purification.

5

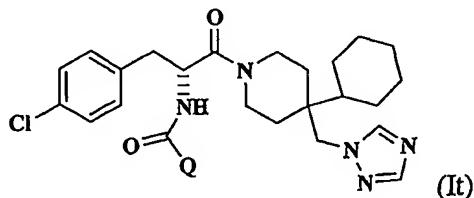
Step B: **Example 252**

To a solution of compound 252A (111 mg, 0.19 mmol) in DCM (5 mL) was added TFA (2.5 mL) at RT. The mixture was stirred at RT for 15 min. and evaporated under reduced pressure. The residue was purified using preparative HPLC and after evaporation, the residue was purified by automated solid phase extraction and concentrated *in vacuo*. The product was dissolved in a 4 M HCl solution in dioxane and lyophilized to yield 70 mg of Example 252 as the hydrochloride salt (66 %). HPLC / MS (L), ret. time = 1.41 min, purity 99 %, MS pos. m/z 487 ($\text{M}+\text{H}$)⁺; HPLC / MS (B), ret. time = 1.43 min, purity 97.8 %, MS pos. m/z 487 ($\text{M}+\text{H}$)⁺; MS (Finigan TSQ 7000, ESI) m/z 487 ($\text{M}+\text{H}$)⁺; IR (ν_{max} , KBr) cm^{-1} 3600-2854, 1683, 1625, 1456; ¹H NMR (400 MHz, MeOH-d₄) δ ppm (two rotamers; 1:1.2 ratio) 9.33 (1H, s), 9.26 (1H, s), 8.53 (1H, s), 8.46 (1H, s), 7.22-7.10 (4H, m), 4.99 (1H, t, J = 8.0 Hz), 4.32 (2H, s, major rotamer), 4.30 (2H, s, minor rotamer), 3.68-3.50 (2H, m), 3.40-3.34 (1H, m), 3.27-3.21 (1H, m), 2.92-2.75 (2H, m), 1.75-0.76 (15H, m).

EXAMPLES 253-54

4-Amino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-butyramide

25



The procedure described for the preparation of Example 252 was used to prepare compounds of formula (I_t), wherein Q has the values listed in Table 13, using N-Boc-3-



amino propionic acid (Ex. 253) and (Ex. 254), in place of N-Boc-glycine.

Compounds were prepared as the hydrochloride salt. In compounds of formula (I),

5 Q=(CR₁₁R₁₂)_y-(CH₂)_x-W.

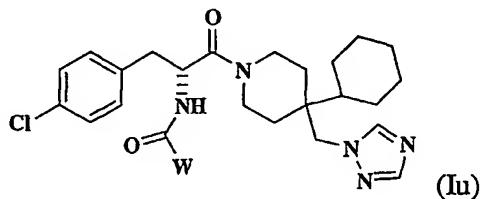
TABLE 13

Ex.	Q	Compound Name	HPLC/MS (ret. time)	¹ H NMR
253	-(CH ₂) ₃ -NH ₂	4-Amino-N-[1-(4-chlorobenzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-butyramide	1.42 ^a min; 1.43 ^b min;	(400 MHz, MeOH-d ₄) δ ppm (two rotamers; 1:2 ratio) 9.30 (1H, s, major rotamer), 9.25 (1H, s, major rotamer), 9.23 (1H, s, minor rotamer), 9.20 (1H, s, minor rotamer), 8.51 (1H, s, major rotamer), 8.47 (1H, s, minor rotamer), 8.45 (1H, s, major rotamer), 8.41 (1H, s, minor rotamer), 7.29-7.09 (4H, m, major and minor rotamers), 4.91 (1H, t, J = 8.0 Hz), 4.31 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 3.61-3.29 (2H, m), 3.40-3.35 (1H, m), 3.27-3.20 (1H, m), 3.05-2.74 (2H, m), 2.36 (1H, d, J = 4 Hz), 2.32 (1H, d, J = 8 Hz), 2.22 (2H, m), 1.95-0.82 (17H, m).

254		1-Methyl-azetidine-2-carboxylic acid[1-(4-chloro-benzyl)-2-(4-cyclohexyl)-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl]-2-oxoethyl]-amide	1.55 ^L min; 1.84 ^m min;	400 MHz, MeOH-d ₄) δ ppm (two rotamers, 1:2) 9.30 (m, 1H, broad), 8.52 (m, 1H, broad), 7.33 (d, 2H, J = 8Hz, major rotamer), 7.28 (d, 2H, J = 8Hz, minor rotamer), 7.24 (d, 2H, J = 8Hz, major rotamer), 7.22 (d, 2H, J = 8Hz, minor rotamer), 5.10 (m, 1H), 4.41 (s, 2H), 4.07-3.93 (m, 2H), 3.72-3.67 (m, 1H), 3.55-3.36 (m, 3H), 3.05-2.90 (m, 2H), 2.88 (s, 3H, major rotamer), 2.86 (s, 2H, minor rotamer), 2.77-2.65 (m, 1H), 2.40-2.19 (m, 1H), 1.80 (m, 3H), 1.68 (m, 3H), 1.54-0.90 (11H, m).
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EXAMPLES 255-303

5

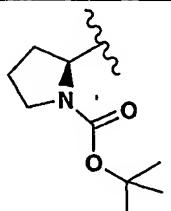
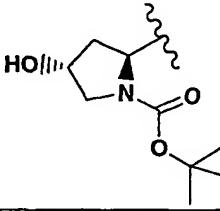
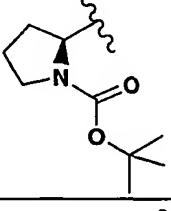
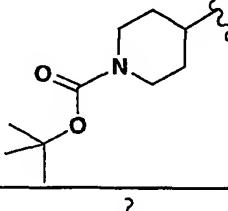
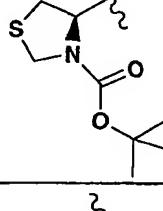
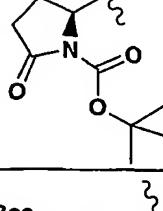
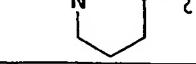


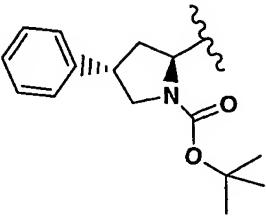
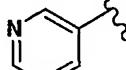
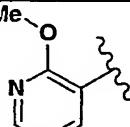
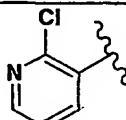
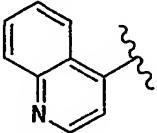
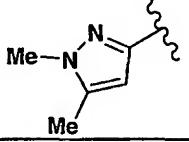
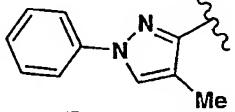
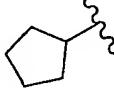
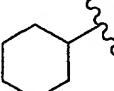
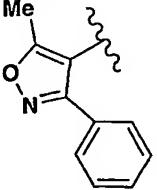
Compounds having the formula (Iu), wherein W has the values listed in Table 14, were prepared following the same or similar procedure described above for Example 171.

10

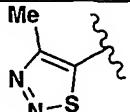
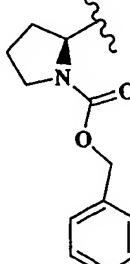
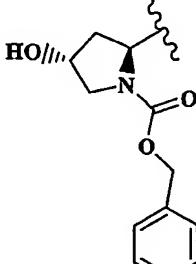
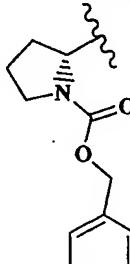
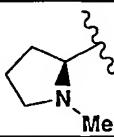
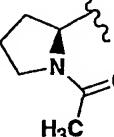
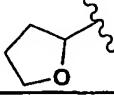
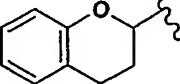
TABLE 14

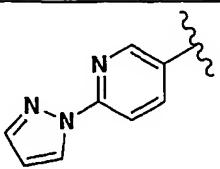
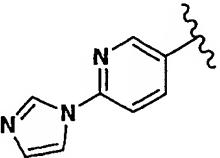
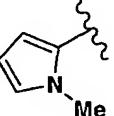
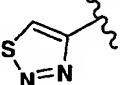
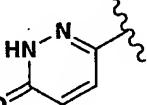
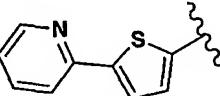
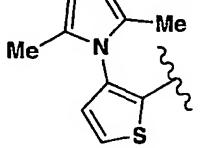
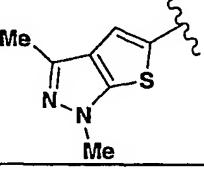
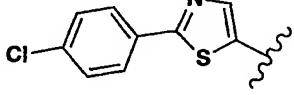
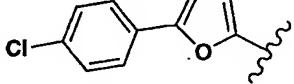
Ex. No.	W	Purity (%)	HPLC ret. time (min)	Mass (M+H)
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255		89.0%	3.9	627.43
256		90.0%	3.7	643.44
257		90.0%	4.0	627.45
258		86.0%	4.0	641.44
259		89.0%	4.0	645.4
260		90.0%	3.7	641.41
261		87.0%	4.1	641.47

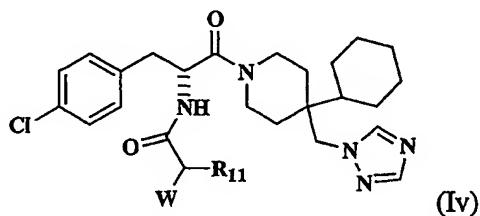
262		90.0%	4.2	703.46
263		91.0%	3.5	535.36
264		94.0%	4.0	565.36
265		93.0%	4.0	569.3
266		97.0%	3.6	585.38
267		96.0%	3.8	552.38
268		94.0%	3.9	614.42
269		91.0%	3.9	526.39
270		91.0%	4.0	540.41
271		92.0%	3.9	615.38

272		90.0%	3.4	542.36
273		92.0%	3.8	540.32
274		93.0%	3.8	540.32
275		91.0%	3.6	583.42
276		93.0%	3.9	570.33
277		86.0%	3.9	665.37
278		98.0%	4.2	622.42
279		94.0%	4.0	677.37
280		92.0%	3.9	566.4
281		92.0%	3.6	525.34
282		93.0%	4.1	664.34

283		91.0%	3.8	556.33
284		92.0%	4.0	661.43
285		92.0%	3.8	677.42
286		92.0%	4.0	661.43
287		83.0%	3.2	541.41
288		91.0%	3.6	569.39
289		88.0%	3.7	528.37
290		93.0%	4.1	590.39

291		92.5%	4.0	601.37
292		83.5%	3.3	601.38
293		87.0%	.7	537.3
294		78.8%	3.7	542.28
295		89.8%	3.6	552.33
296		92.1%	3.9	617.34
297		90.6%	4.2	633.38
298		92.6%	3.9	608.36
299		93.2%	4.4	651.3
300		88.7%	4.3	634.33

301		92.8%	3.5	585.4
302		93.4%	3.5	541.36
303		93.8%	3.9	611.45

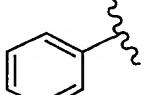
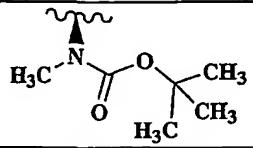
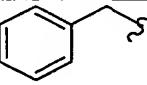
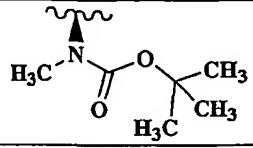
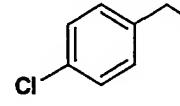
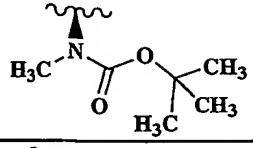
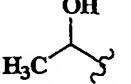
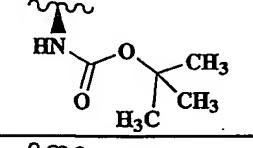
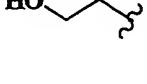
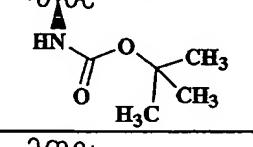
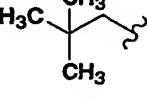
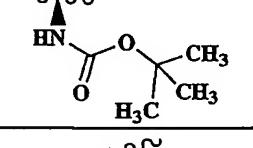
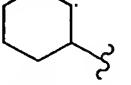
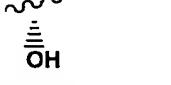
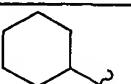
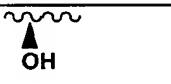
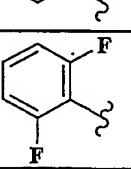
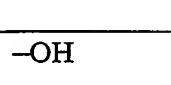
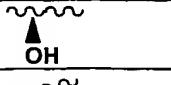
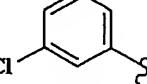
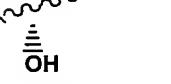
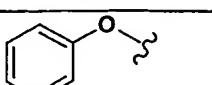
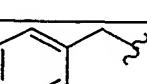
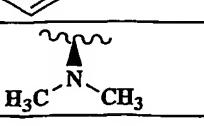
EXAMPLES 304-319

Compounds having the formula (Iv), wherein R₁₁ and W have the values listed in Table 15, were prepared following the same or similar procedure described above for Example 171.

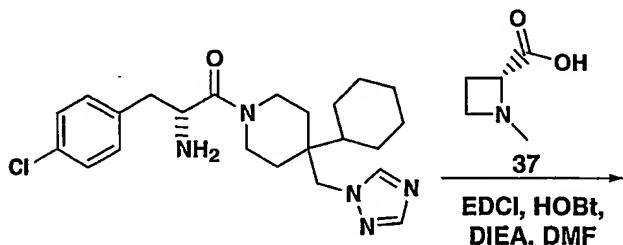
10

TABLE 15

Ex. No.	R ₁₁	W	Purity (%)	HPLC ret. time (min)	Mass (M+H)
304	-CH ₃		92.0%	4.0	615.43
305	-isoPr		88.0%	4.2	643.46

306			91.0%	4.2	677.45
307			89.0%	4.3	691.48
308			90.0%	4.4	725.43
309			90.0%	3.9	631.43
310			82.0%	3.8	631.43
311			90.0%	4.2	657.49
312			91.0%	4.1	570.41
313			92.0%	4.0	570.41
314			86.0%	3.7	600.36
315	-isoPr		91.0%	3.8	544.39
316			91.0%	4.0	598.33
317	Et		92.0%	4.1	592.4
318			85.0%	3.5	605.43

1-Methyl-azetidine-2-carboxylic acid[1-(4-chloro-benzyl)-2-(4-cyclohexyl)-1,2,4-triazol-1-ylmethyl-piperidin-1-yl]-2-oxo-ethyl]-amide (38)



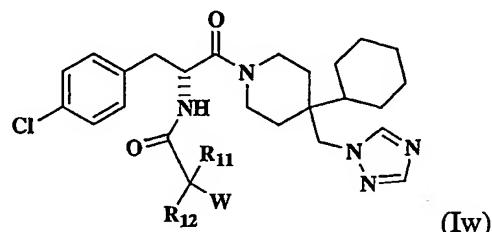
1 (BMS-500721)

38. BMS-568248

Scheme 18

319			91.4%	3.9	631.43
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EXAMPLES 320-322



5

Compounds having the formula (Iw), wherein R₁₁ and W have the values listed in Table 16, were prepared following the same or similar procedure described above for Example 171.

10

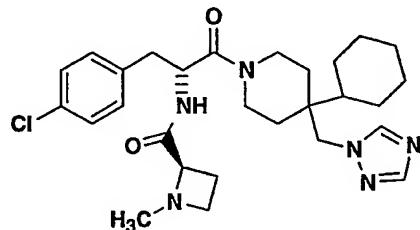
TABLE 16

Ex. No.	R ₁₁	R ₁₂	W	Purity (%)	HPLC ret. time (min)	Mass (M+H)
320	CH ₃	Et	-OH	62.0%	3.7	530.38
321	CH ₃	Ph		94.0%	4.0	578.38
322	CH ₃	Ph		93.0%	3.8	578.38

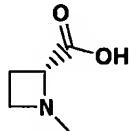
EXAMPLE 323

1-Methyl-azetidine-2-carboxylic acid[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-amide

5



To a solution of 2-Amino-3-(4-chloro-phenyl)-1-(4-cyclohexyl-4-[1,2,4]triazol-1-
10 ylmethyl-piperidin-1-yl)-propan-1-one (Compound 171A) (79 mg, 0.18 mmol) and (R)-1-



methyl-azetidine-2-carboxylic acid 37 (32 mg, 0.28 mmol) in N,N-dimethylformamide (1.8 mL) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (53 mg, 0.28 mmol), 1-hydroxybenzotriazole hydrate (37 mg, 0.28 mmol) and N,N-diisopropylethylamine (97 µL, 0.56 mmol) at rt. The mixture was stirred 12 hours and
15 then the solution was purified using preparative HPLC (Column: Column S-5 Phenyl 20 x 100 mm. Acetonitrile-0.05% TFA/water: 7 min. gradient from 10% AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min.) and collected fractions were concentrated in vacuo. A second purification using preparative HPLC was done (Column: Column X-Terra C-8 21.2 x 100 mm. Acetonitrile- 5 mM NH₄OAc/water: 7 min. gradient from 10%
20 AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min) and collected fractions were concentrated in vacuo. The hydrochloride salt was made using a solution of 4 M HCl in dioxane and the salt was lyophilized to yield 30 mg of Example 323. (31 %). HPLC / MS (Column: Xterra- C8 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH₃CN - 90 %H₂O – 5mM NH₄OAc; Solvent B: 90% CH₃CN - 10%
25 H₂O – 5mM NH₄OAc; UV: 220 nm; Micromass ZMD 2000, ESI): retention time 1.55 min, purity 92.4 %, MS pos. m/z 527 (M+H)⁺; HPLC / MS (Column: YMC-Pack S5

Phenyl 4.6 x 50 mm; Flow rate: 3 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH₃CN - 90 %H₂O – 0.05 % TFA; Solvent B: 90% CH₃CN - 10 %H₂O – 0.05 % TFA; UV: 220 nm; Micromass ZMD 2000, ESI): retention time 1.83 min, purity 97.5 %, MS pos. *m/z* 527 (M+H)⁺; MS (Finigan TSQ 7000, ESI) *m/z* 527 (M+H)⁺; HRMS

- 5 calculated for: C₂₈H₃₉ClN₆O₂ (M + H⁺) = 527.290128; Found = 527.291621; ¹H nmr (400 MHz, MeOH-d₄) δ ppm (two rotamers, 1:2) 9.60 (s, 1H, broad, minor rotamer), 9.57 (s, 1H, broad, major rotamer), 8.81 (dd, 1H, J = 4, 8 Hz), 8.74 (s, 1H, broad, minor rotamer), 8.69 (s, 1H, broad, major rotamer), 7.34-7.23 (m, 4H), 5.08 (m, 1H), 4.46 (s, 2H, major rotamer), 4.44 (s, 2H, minor rotamer), 4.16-3.97 (m, 2H), 3.77-3.60 (m, 2H),
10 3.52-3.46 (m, 1H), 3.40-3.35 (m, 1H), 2.99 (d, 1H, J = 8 Hz), 2.89 (s, 3H, major rotamer), 2.85 (s, 3H, minor rotamer), 2.80-2.71 (m, 1H), 2.54-2.45 (m, 1H), 1.80 (m, 3H), 1.68 (m, 3H), 1.54-0.90 (m, 11H).

15

20

25

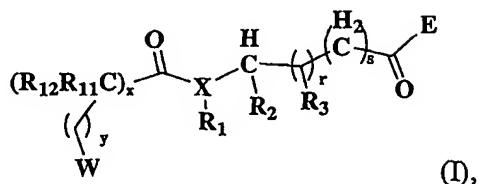
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35

CLAIMS

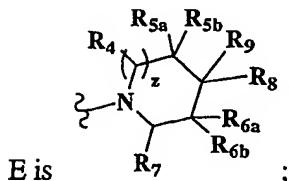
We claim:

- 5 1. A compound according to formula (I),



10 or a pharmaceutically-acceptable salt, hydrate or prodrug thereof,

in which



- 15 X is N or CH;

R₁ is hydrogen or C₁₋₆alkyl or is joined together with R₂ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R_2 is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo; or C_{1-6} alkyl or C_{2-6} alkenyl
 optionally substituted with one to three of hydroxy, alkoxy, halogen, cyano, nitro,
 trifluoromethyl, amino, alkylamino, aryl, cycloalkyl, heteroaryl, and/or
 heterocyclo; or R_1 is joined together with R_2 or R_3 to form a monocyclic or
 bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₃ is hydrogen or C₁₋₆alkyl or is joined together with R₂ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

- 25 R₄, R₅, R_{5a} R_{5b}, R₆, R_{6a}, R_{6b}, and R₇ are independently selected from hydrogen, alkyl, substituted alkyl, halogen, hydroxy, alkoxy, keto, aryl, heteroaryl, cycloalkyl, and heterocyclo, or R_{5a} and/or R_{5b}, R_{6a} and/or R_{6b}, are joined together with R₈ or R₉ to form a fused carbocyclic, heterocyclic or heteroaryl ring;

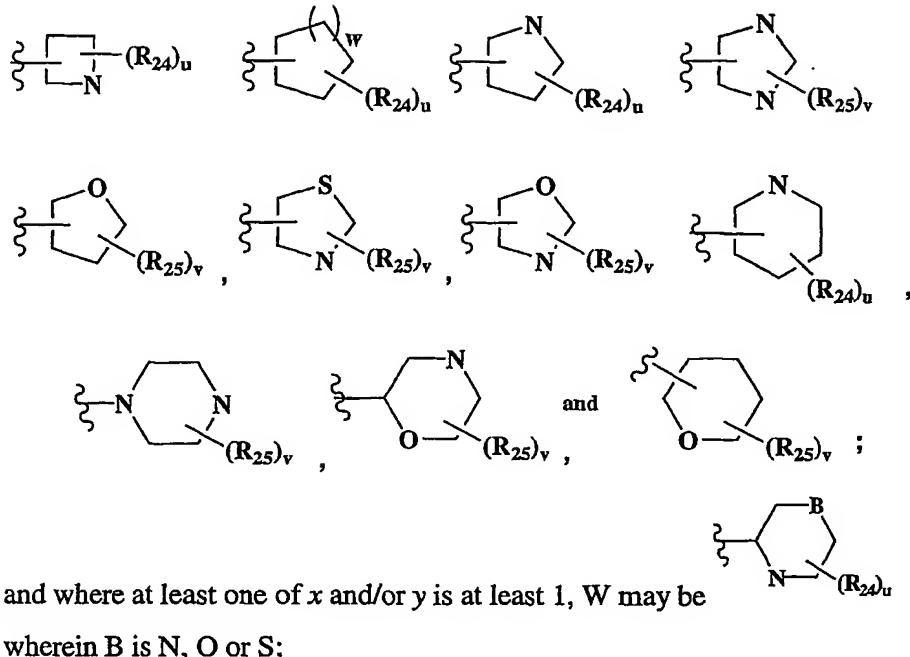
R₈ and R₉ are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, -OR₁₃, -NR₁₃R₁₄, -SR₁₃ -S(O)_pR₁₄, -C(=O)R₁₃, -OC(=O)R₁₃, -CO₂R₁₃, -C(=O)NR₁₃R₁₄, -NR₁₃C(=O)R₁₄, -OC(=O)NR₁₃R₁₄, -NR₁₃CO₂R₁₄, -NR₁₃C(=O)NR₁₄R₁₅ or -NR₁₃SO₂R₁₄; or R₈ and R₉ taken together form a monocyclic or bicyclic cycloalkyl or heterocyclo joined in a spiro fashion to ring E at C*, provided that R₈ and R₉ are not both hydrogen, and provided further that when R₈ is -OR₁₃, -(CH₂)_k-aryl or -(CH₂)_k-heteroaryl, then R₉ is not -C(=O)NR₁₈R₁₉, -CO₂R₁₉, -(CH₂)_mNR₁₈SO₂R₂₀, -(CH₂)_mNR₁₈C(=O)R₂₀, -(CH₂)_mOR₁₉, -(CH₂)_mO(C=O)R₂₀, -CH(R₁₈)R₁₉, or -(CH₂)_mNR₁₈(C=O)NR₁₉R₂₁;

R₁₁ and R₁₂ are selected independently of each other from hydrogen, alkyl, halogen, hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl, cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, and where y is at least 1, then R₁₁ and R₁₂ may be heterocyclo or heterocycloalkyl, or R₁₁ and R₁₂, when attached to the same carbon atom, may join to form a spirocycloalkyl ring;

R₁₃, R₁₄ and R₁₅ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heterocyclo, or heteroaryl; or R₁₃ and R₁₄, or R₁₄ and R₁₅ may join together to form a heterocyclo or heteroaryl, except R₁₄ is not hydrogen when joined to a sulfonyl group as in -S(O)_pR₁₄ or -NR₁₃SO₂R₁₄;

W is selected from:

- 4) -NR₁₆R₁₇, -NR₁₆C(=O)R₂₂, -NR₁₆CO₂R₂₂, -OR₂₃, amidino, and guanidino;
- 5) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said heteroaryl and heterocyclo groups may be substituted or unsubstituted and may have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused thereto; or
- 6) a ring selected from:



- 5 R_{16} and R_{17} are selected from hydrogen, alkyl and substituted alkyl;
 R_{18} , R_{19} and R_{21} are independently hydrogen or C_{1-6} alkyl optionally substituted with halogen;
- 10 R_{20} is C_{1-6} alkyl, aryl, or heteroaryl;
 R_{22} and R_{23} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclo;
- 15 R_{24} and R_{25} at each occurrence are attached to any available carbon or nitrogen atom of W and at each occurrence are selected from hydrogen, C_{1-6} alkyl, halogen, substituted C_{1-6} alkyl, amino, alkylamino, cyano, nitro, trifluoromethoxy, $-C(=O)R_{26}$, $-CO_2R_{26}$, $-SO_2R_{26}$, $-OR_{26}$, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R_{25} attached to two adjacent nitrogen or carbon atoms may join to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R_{24} or two R_{25} when attached to the same carbon atom may form keto ($=O$);
- 20 R_{26} is hydrogen, alkyl, substituted alkyl, aryl, heterocyclo, cycloalkyl, or heteroaryl, except when joined to a sulphonyl group as in SO_2R_{26} , then R_{26} is not hydrogen;
- 25 k and m are independently 0, 1, 2 or 3;

p is 1, 2, or 3;

r is 0 or 1;

s is 0 or 1;

u and *v* are 0, 1, 2, or 3;

5 *w* is 0, 1, or 2;

x and *y* are 0, 1, 2, 3, or 4; and

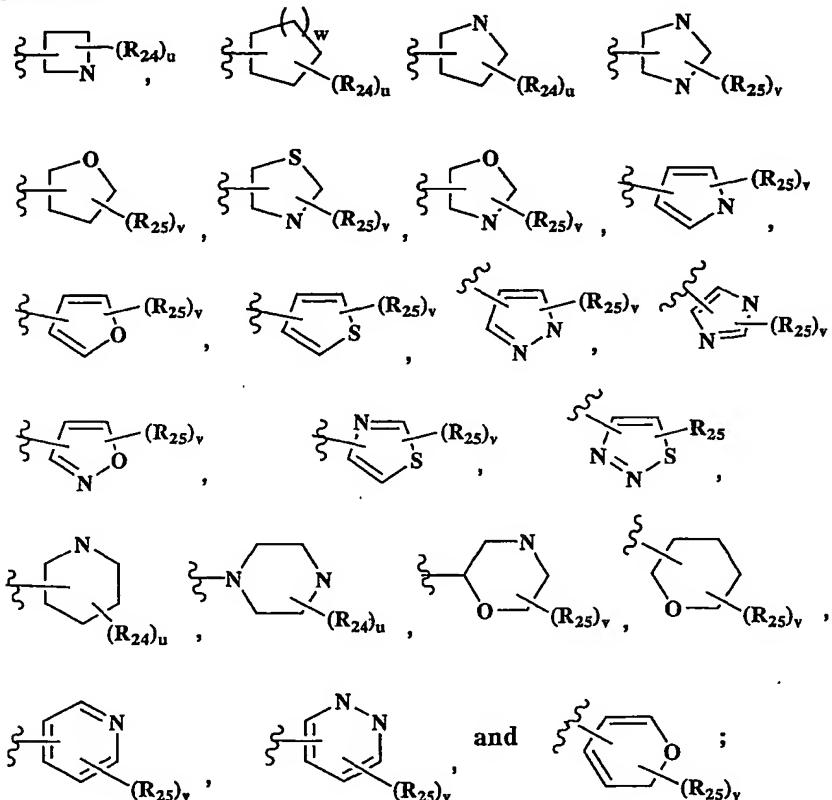
z is 0, 1, or 2.

10

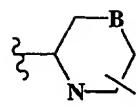
2. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

W is $-\text{NR}_{16}\text{R}_{17}$, $-\text{NHC}(=\text{O})\text{R}_{22}$, $-\text{NHCO}_2\text{alkyl}$, or OR_{23} ; or

W is a ring selected from:



15



and where at least one of x and/or y is at least 1, W may be
N, O or S;

R_{16} and R_{17} are independently selected from hydrogen, C_{1-8} alkyl, and $(CH_2)_q-J$, wherein J is selected from naphthyl, furanyl, indolyl, imidazolyl, pyrimidinyl,
5 benzothiophenyl, pyridinyl, pyrrolyl, pyrrolidinyl, thiophenyl, and C_{3-7} cycloalkyl,
wherein the alkyl, alkylene, and/or J groups of R_{16} and/or R_{17} are optionally substituted with up to three R_{32} ;

R_{24} is selected from keto (=O), C_{1-6} alkyl, halogen, amino, aminoalkyl, alkylamino,
hydroxy, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, $-C(=O)$ alkyl, $-C(=O)$ aminoalkyl,
10 $-C(=O)$ phenyl, $-C(=O)$ benzyl, $-CO_2$ alkyl, $-CO_2$ phenyl, $-CO_2$ benzyl, $-SO_2$ alkyl,
 $-SO_2$ aminoalkyl, $-SO_2$ phenyl, $-SO_2$ benzyl, phenyl, benzyl, phenoxy,
benyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl,
and each R_{24} in turn is optionally substituted with one to two R_{31} ;

R_{25} at each occurrence is attached to any available carbon or nitrogen atom of W and is
15 selected from C_{1-6} alkyl, halogen, amino, aminoalkyl, alkylamino, hydroxy, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, $-C(=O)$ alkyl, $-C(=O)$ aminoalkyl, $-C(=O)$ phenyl,
 $-C(=O)$ benzyl, $-CO_2$ alkyl, $-CO_2$ phenyl, $-CO_2$ benzyl, $-SO_2$ alkyl,
 $-SO_2$ aminoalkyl, $-SO_2$ phenyl, $-SO_2$ benzyl, phenyl, benzyl, phenoxy,
benyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl,
20 and/or two R_{25} when attached to adjacent carbon and/or nitrogen atoms may be taken together to form a fused benzo or pyrazolyl ring, and/or two R_{25} when attached to the same carbon atom (in the case of a non-aromatic ring) may form keto (=O), and each R_{25} in turn is optionally substituted with up to two R_{31} ;

R_{22} is selected from C_{1-6} alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl,
25 phenyl, pyrrolylalkyl, piperidinyl, and piperidinylalkyl, wherein R_{22} in turn is optionally substituted with one to two C_{1-4} alkyl and/or $-CO_2(C_{1-4}$ alkyl);

R_{23} is hydrogen or phenyl;

R_{31} is selected from halogen, trifluoromethyl, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

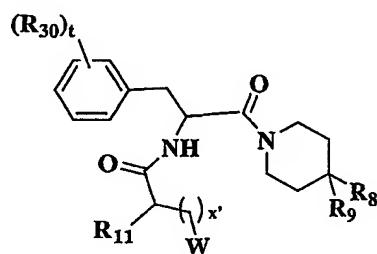
R₃₂ is selected from C₁₋₆alkyl, hydroxy, C₁₋₄alkoxy, amino, C₁₋₄alkylamino, aminoC₁₋₄alkyl, trifluoromethyl, halogen, phenyl, benzyl, phenoxy, benzyloxy, -C(=O)(CH₂)NH₂, -CO₂(C₁₋₄alkyl), -SO₂(C₁₋₄alkyl), tetrazolyl, piperidinyl, pyridinyl, and indolyl, wherein when R₃₂ is a ring, said ring in turn is optionally substituted with one to two C₁₋₄alkyl, hydroxy, methoxy, and/or halogen; and

5 q is 0, 1, 2 or 3;

w is selected from 0, 1, or 2; and

u and v are selected from 0, 1, and 2.

10 3. A compound according to claim 2, or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof, having the formula:



15 in which

R₈ and R₉ are selected independently from hydrogen, alkyl, -(CH₂)_j-C(=O)alkyl, -(CH₂)_j-phenyl, -(CH₂)_j-naphthyl, -(CH₂)_j-C₄₋₇cycloalkyl, -(CH₂)_j-heterocyclo, and -(CH₂)_j-heteroaryl, or R₈ and R₉ together form a spirocycloalkyl or spiroheterocyclic ring; and

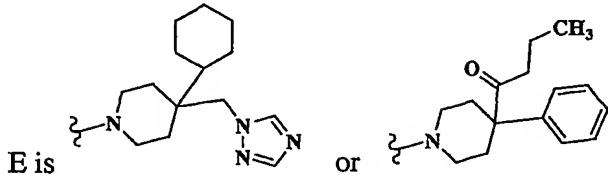
20 R₃₀ is selected from C₁₋₄alkyl, hydroxy, alkoxy, halogen, nitro, cyano, amino, alkylamino, phenyl, and -C(=O)phenyl;

j is selected from 0, 1, 2 and 3;

t is 0, 1 or 2; and

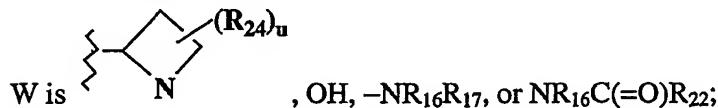
x' is 0, 1 or 2.

4. A compound according to claim 3, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which



5

5. A compound according to claim 3, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which



10 R₁₆ and R₁₇ are selected from hydrogen and C₁₋₄alkyl;

R₂₄ is C₁₋₄alkyl; and

u is 0 or 1.

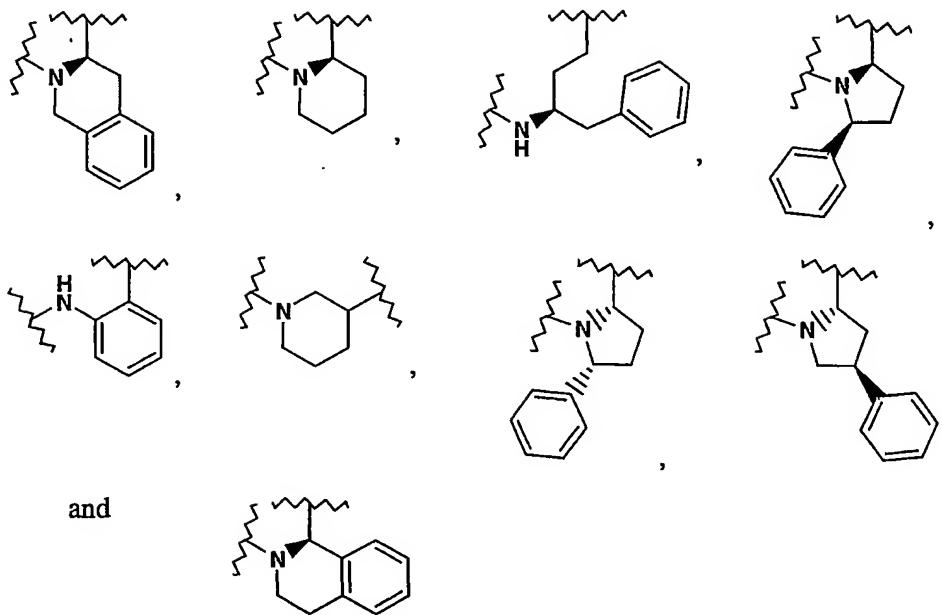
15 6. A compound according to claim 5, or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof, in which

R₁₁ is hydrogen or imidazolylC₁₋₄alkyl, in which the imidazolyl in turn is optionally substituted with lower alkyl;

R₁₂ is hydrogen or C₁₋₄alkyl; and

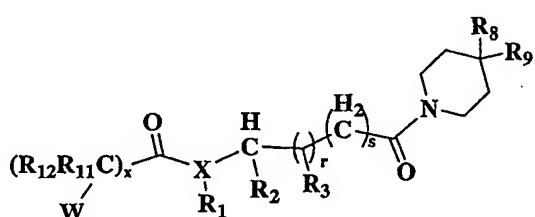
20 x' is 1 or 2.

7. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof, in which -X(R₁)-CH(R₂)-CH(R₃)_r-(CH₂)_s-, taken together are selected
25 from C₁₋₄alkylene,



8. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof, in which R₁₆ and R₁₇ are independently selected from hydrogen, C₁-₈alkyl, and C₁-₈substituted alkyl, except R₁₆ and R₁₇ are not alkyl substituted with pyridyl, imidazolyl, thiazolyl, pyrimidinyl, and piperazinyl, and W is not morpholinyl.
- 5
9. A compound according to the formula,

10



or a pharmaceutically-acceptable salt, hydrate or prodrug thereof,

15

in which

X is N or CH;

R₁ is hydrogen or C₁₋₆alkyl or is joined together with R₂ or R₃ to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₂ is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo, or C₁₋₆alkyl or C₂₋₆alkenyl
5 optionally substituted with one to three of hydroxy, halogen, aryl, cycloalkyl,
 heteroaryl, and/or heterocyclo; or R₁ is joined together with R₂ or R₃ to form a
 monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R₃ is hydrogen or C₁₋₆alkyl or is joined together with R₂ to form a monocyclic or bicyclic
 aryl, cycloalkyl, heteroaryl or heterocycle;

R₈ and R₉ are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl,
10 alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, -OR₁₃, -NR₁₃R₁₄, -SR₁₃
 -S(O)_pR₁₄, -C(=O)R₁₃, -OC(=O)R₁₃, -CO₂R₁₃, -C(=O)NR₁₃R₁₄, -NR₁₃C(=O)R₁₄,
 -OC(=O)NR₁₃R₁₄, -NR₁₃CO₂R₁₄, -NR₁₃C(=O)NR₁₄R₁₅ or -NR₁₃SO₂R₁₄; or R₈ and
 R₉ taken together form a monocyclic or bicyclic cycloalkyl or heterocyclo joined
 in a spiro fashion to ring E at C*,

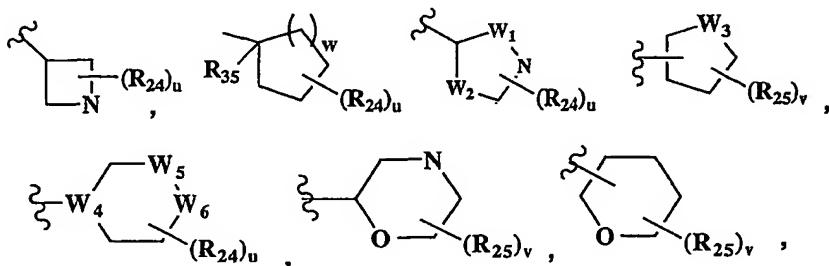
15 R₁₁ and R₁₂ are selected independently of each other from hydrogen, alkyl, halogen,
 hydroxy, hydroxylalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl,
 cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, or R₁₁ and R₁₂, when
 attached to the same carbon atom, may join to form a spirocycloalkyl ring;

R₁₃, R₁₄ and R₁₅ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl,
20 heterocyclo, or heteroaryl; or R₁₃ and R₁₄, or R₁₄ and R₁₅ may join together to
 form a heterocyclo or heteroaryl, except R₁₄ is not hydrogen when joined to a
 sulfonyl group as in -S(O)_pR₁₄ or -NR₁₃SO₂R₁₄;

W is selected from:

- 1) -NR₁₆R₁₇, -NR₁₆C(=O)R₂₂, -NR₁₆CO₂R₂₂, or -OR₂₃; or
- 25 heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl,
 imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl,
 pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein
 said heteroaryl and heterocyclo groups may be optionally substituted with one
 to three R₃₆, and may have an optionally-substituted carbocyclic, heterocyclic
30 or heteraryl ring fused thereto; or

3) a carbocyclic, heterocyclic, or heteroaryl ring selected from:



in which W_1 and W_2 are NH, CH₂, O or S, W_3 is O or S, W_4 is N or CH, and W_5

5 and W_6 are NH or CH₂, wherein when W_1 , W_2 , W_5 and W_6 are NH or CH₂, said groups are optionally substituted with R_{24} ;

R_{16} and R_{17} are C₁₋₈alkyl or (CH₂)_q-J, wherein J is selected from aryl, heteroaryl, heterocyclo, or cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R_{16} and/or R_{17} are optionally substituted with up to three R_{32} ;

10 R_{22} is selected from C₁₋₆alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrrolylalkyl, piperidinyl, and piperidinylalkyl, wherein R_{22} in turn is optionally substituted with one to two C₁₋₄alkyl and/or -CO₂(C₁₋₄alkyl);

R_{23} is hydrogen or aryl;

15 R_{24} and R_{25} at each occurrence are attached to any available carbon or nitrogen atom of W and at each occurrence are selected from hydrogen, C₁₋₆alkyl, halogen, substituted C₁₋₆alkyl, amino, alkylamino, -C(=O)R₂₆, -CO₂R₂₆, -SO₂R₂₆, -OR₂₆, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R_{25} attached to two adjacent nitrogen or carbon atoms may join to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R_{24} or two R_{25} when attached to the same carbon atom may form keto (=O);

20 R_{26} is hydrogen, alkyl, phenyl, benzyl, or aminoalkyl, except when joined to a sulphonyl group as in SO₂R₂₆, then R_{26} is not hydrogen;;

25 R_{32} is selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy, halogen, nitro, phenyl, benzyl, phenoxy, benzyloxy, -C(=O)phenyl, amino, alkylamino, and aminoalkyl, wherein when R_{32} includes a phenyl group said phenyl group in turn is optionally substituted with one to two of halogen, nitro, cyano, C₁₋₄ alkyl, and/or C₁₋₄ alkoxy;

R_{36} at each occurrence is selected from C_{1-6} alkyl, halogen, substituted C_{1-6} alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, acyl, carboxyalkyl, sulfonyl, aryl, heteroaryl, heterocyclo, and cycloalkyl;

j is selected from 0, 1, 2 and 3;

5 r is 0 or 1;

s is 0 or 1;

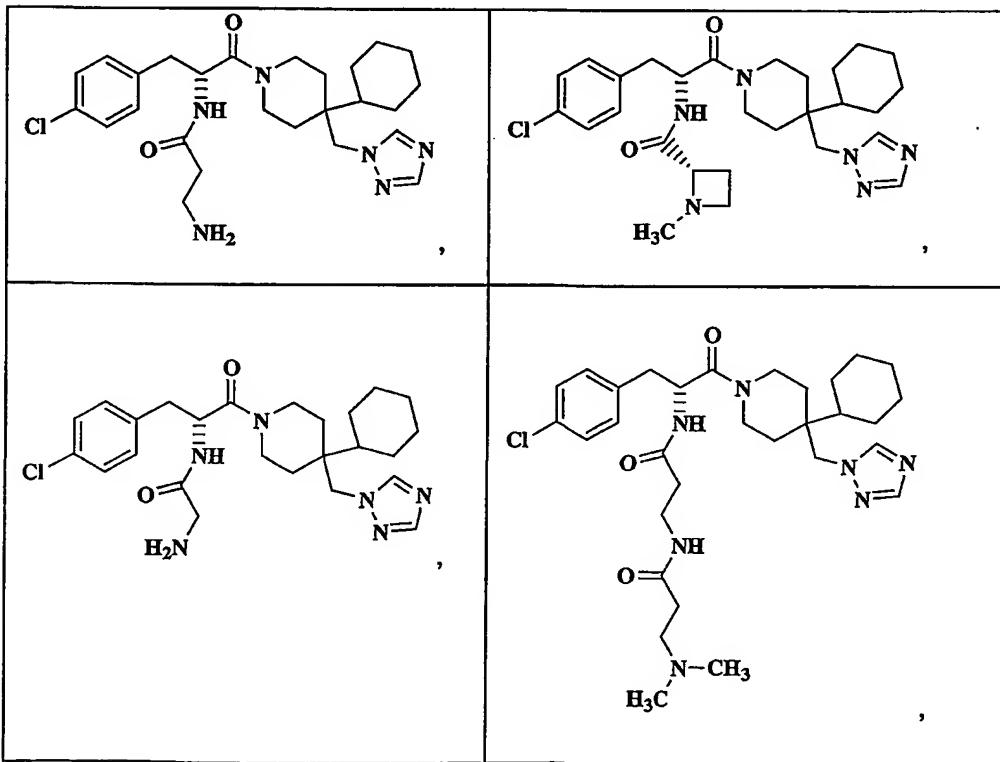
u and v are 0, 1, or 2;

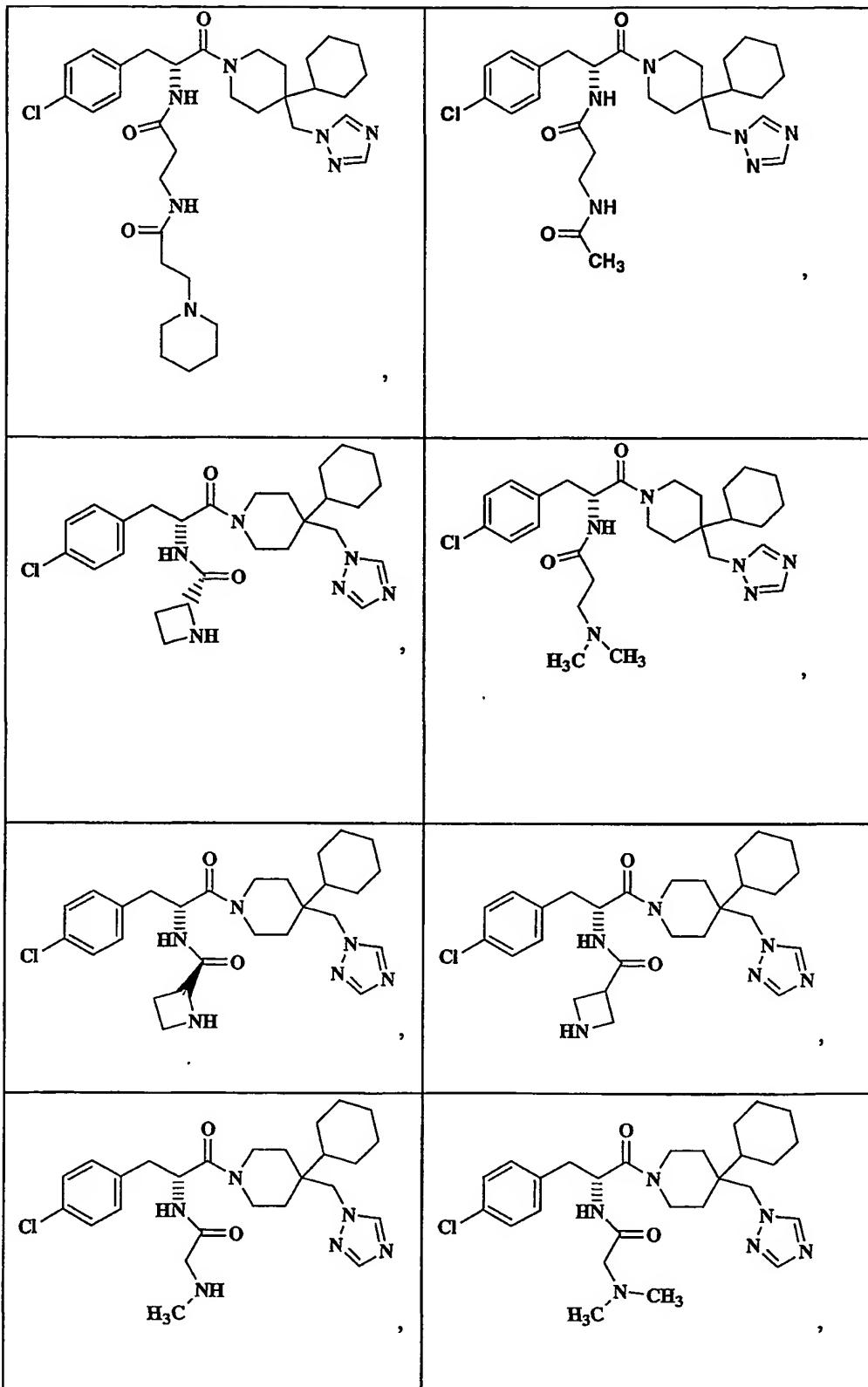
w is 0, 1, or 2; and

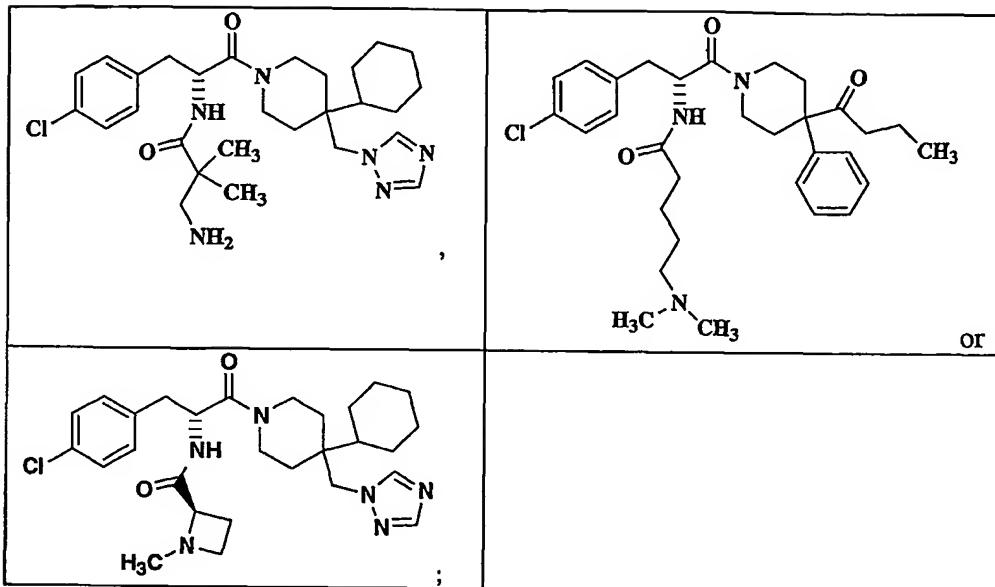
x is 0, 1, 2, 3, or 4.

10

10. A compound according to claim 1, having (i) the formula,







or (ii) a pharmaceutically-acceptable salt, hydrate or prodrug thereof.

5

11. A pharmaceutical composition comprising at least one compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, a pharmaceutically-acceptable salt, hydrate, or prodrug thereof; and a pharmaceutically-acceptable carrier or diluent.

10

12. A pharmaceutical composition comprising (i) at least one compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, a pharmaceutically-acceptable salt, hydrate, or prodrug thereof; (ii) at least one second compound effective 15 for treating an inflammatory or immune disease; and (iii) a pharmaceutically-acceptable carrier or diluent.

13. Use of a compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof, for treating a 20 melanocortin-receptor associated condition.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079146 A3

(51) International Patent Classification⁷: **A61K 31/44, 31/445, 31/505, C07D 401/12, 401/14, 403/12, 403/14**

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(21) International Application Number: **PCT/US02/06581**

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(22) International Filing Date: **2 March 2002 (02.03.2002)**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(25) Filing Language: **English**

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: **English**

Published:

— *with international search report*

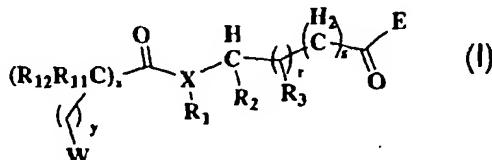
(30) Priority Data:
60/273,206 2 March 2001 (02.03.2001) US
60/273,291 2 March 2001 (02.03.2001) US

(88) Date of publication of the international search report:
6 February 2003

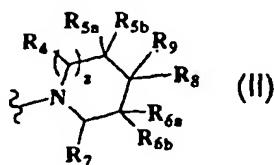
(71) Applicant (*for all designated States except US*): **BRISTOL-MYERS SQUIBB COMPANY [US/US]**; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS USEFUL AS MODULATORS OF MELANOCORTIN RECEPTORS AND PHARMACEUTICAL COMPOSITIONS COMPRISING SAME



(57) Abstract: Compounds having the formula (I), and pharmaceutically-acceptable salts, hydrates and prodrugs thereof, in which E is formula (II), X is N or CH, W is -NR₁₆R₁₇, -NR₁₆C(=O)R₂₂, -NR₁₆CO₂R₂₂, -OR₂₃, or a heteroaryl or heterocyclo group as defined in the specification, and R₁ through R₁₂, R₁₆, R₁₇, R₂₂, R₂₃, x, y, and z are as defined in the specification, are useful as modulators of melanocortin receptors, particularly MC-1R and MC-4R.



WO 02/079146 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/06581

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/256, 278, 318, 319, 322, 323, 326; 544/60, 129, 349, 360; 546/17, 193, 199, 201, 205, 209, 210

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS—structure

EAST/WEST—subclass image

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US 2002/0019523 A1 (PALUCKI et al.) 14 February 2002, see entire document, especially pages 9-57 scheme 3.	1-6, 8-13
Y	US 2001/0029259 A1 (NARGUND et al.) 11 October 2001, see entire document, especially pages 22-27, examples 1-34.	1-6, 8-9, 11-12
Y	US 5,936,089 (CARPINO et al.) 10 August 1999, see entire document, especially column 3-4 description with col. 79, example 21.	1-6, 8-9, 11-12
Y	US 5,492,916 A (MORRIELLO et al.) 20 February 1996, see entire document, especially col. 49, Table Ib and col. 118, Table XI, and abstract.	1-6, 8-9, 11-13

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
"	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
11 SEPTEMBER 2002	17 OCT 2002

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <i>Jayne Bridges</i> CELIA CHANG Telephone No. (703) 308-1235
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/06581

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-6, 8-9, 11-13 reading on claim 10

Remark on Protest



The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/06581

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7): A61K 31/44, 31/445, 31/505; C07D 401/12, 401/14, 403/12, 403/14

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/256, 278, 318, 319, 322, 323, 326; 544/60, 129, 349, 360; 546/17, 193, 199, 201, 205, 209, 210

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

Group I, claims 1-6, 8-9, 11-13 (in part) and 10, drawn to R₁, R₂ are independent substituents, X(R₁)-CHR₂-CHR₃, does not form rings.

Group II, claims 1-6, 8-9, 11-13 (in part) and 7, drawn to R₁, R₂ are independent substituents, X(R₁)-CHR₂-CHR₃, forms ring.

Group III, claims 1-6, 8-9, 11-13 (in part) drawn to spiro compounds when R₁-R₂ forms a ring.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Compounds of groups I-III do not share substantial structural feature as to form one inventive concept. In Annex B of the Administrative Instructions, with respect to Markush Practice, it was stated (see Part(f)(i)(B)1 and (f)ii) that "Significant structural elements is....the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art" and "if it can be shown that at least one Markush alternative is not novel over the prior art" then the question of unity of invention shall be reconsidered by the examiner.

It is evidenced that, at least one Markush alternative is not novel in the instant claims see Carpino et al. CA 126, RN 185056-27-3 anticipates claim 1, group I.